Neuropsychiatric Disease and Treatment

Dovepress
Taylor & Francis Group

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REVIEW

Acupuncture for Parkinson's Disease: A Narrative Review of Clinical Efficacy and Mechanistic Insights

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Abstract: Parkinson's disease (PD) has been recognized for more than two centuries. Historically viewed as a clinicopathological entity, PD may have diverse genetic or environmental factors that initiate the disease through various, albeit partially overlapping, pathways. The disease manifests both motor and non-motor symptoms, which may occur individually or concurrently, with a tendency to gradually worsen and intensify as the disease progressed. Together, PD poses rapidly escalating healthcare challenges with profound global repercussions. Encouragingly, PD is treatable, particularly when the interventions are tailored through a personalized approach. In recent years, acupuncture, a cornerstone of traditional Chinese medicine, has garnered widespread acceptance as a therapeutic intervention for PD, demonstrating clinically meaningful effects across multiple domains—including motor symptoms (eg, tremor and bradykinesia), non-motor manifestations (eg, sleep disturbances and depression), and cognitive impairment—based on accumulating evidence from both mechanistic and clinical studies. Elucidating the therapeutic mechanisms and clinical efficacy of acupuncture in PD could substantially enhance treatment alternatives. While accumulating evidence supports its benefits, several critical research gaps persist including comparative effectiveness among acupuncture modalities (eg, manual versus electroacupuncture) in modifying disease progression; sustained neuroprotective effects versus transient symptomatic improvement; and development of standardized protocols tailored to distinct motor and non-motor symptom profiles. Methodical investigation of these aspects may yield more targeted, evidence-based interventions for PD management. This narrative review synthesizes evidence from PubMed, Web of Science, CNKI, VIP, Wanfang, and CBM, to examine the application of acupuncture in PD, subsequently summarized the available evidence supporting its utilization and outlined the mechanisms by which acupuncture may exert its therapeutic effects. These mechanisms include preventing the accumulation of α-synuclein in dopaminergic neurons, mitigating apoptosis and oxidative stress, modulating dopamine-related neuroinflammation, and regulating the circuits surrounding dopaminergic neurons in the ganglia. Our study provides the comprehensive integration of clinical and preclinical evidence, which offers a mechanistic explanation for acupuncture's therapeutic benefits while identifying optimal treatment protocols for clinical application. In summary, acupuncture shows significant potential as an effective treatment for PD.

Keywords: Parkinson's disease, acupuncture, effectiveness, mechanism

Introduction

Parkinson's disease (PD), a complex neurological condition stemming from various causes and diverse clinical presentations, ranks as the second most common neurodegenerative disorder worldwide. It has escalated into a significant societal concern and a global priority that demands attention.[1] In 1817, James Parkinson first described PD in his "Essay on The Shaking Palsy", characterized the clinical syndrome by resting tremor, bradykinesia, rigidity, postural instability, and a range of both motor and non-motor symptoms.[2] Over the past three decades, the PD-incidence has surged by 2.5 times, elevating it to be one of the primary causes of neurological dysfunction. The Global Burden of Disease Study predicts a dramatic rise in PD cases, from approximately 7 million in 2015 to an alarming figure of nearly 13 million by 2040, indicating a looming "PD epidemic".[3]

Received: 2 April 2025
Accepted: 1 August 2025
Published: 22 August 2025

The precise etiology of PD remains elusive, yet extensive research indicates that genetic factors, environmental exposures, and their intricate interplay are the primary contributors.[4] The heritability of PD, derived from twin studies and genetic analyses, is estimated to range between 22% and 40%.[1] Notably, a robust genetic component has been identified, with over 90 associated loci serving as risk factors.[5] Additionally, environmental factors, such as prolonged exposure to toxins or cumulative harm over time, are thought to contribute to the disease's development across diverse populations. Other risk factors include age, which remains the most prominent, and gender, as men are more susceptible than women, with an approximate male-to-female ratio of 3:2.[6]

Beyond the cardinal motor symptoms of PD—namely bradykinesia, rigidity, resting tremor, and postural instability—additional non-motor manifestations including mood and cognitive impairments (eg, anxiety, depression, emotional fluctuations), autonomic dysfunction (manifesting as urinary incontinence, constipation, dysphagia, orthostatic hypotension), and sleep disorders significantly impact patients' quality of life.[7] These symptoms profoundly impact the-quality-life of patients, ultimately contributing to a progressive rise in disability. Beyond its direct impact on patients, PD also exerts a significant toll on caregivers, predominantly resulting in excessive stress among them.[8] Additionally, for society at large, PD represents a growing socio-economic burden.[3] Hence, there is an urgent need for comprehensive public health strategies to address both the healthcare and societal demands faced by individuals with PD. Current Western medical management relies on "cocktail therapy"—combinations of levodopa, dopamine agonists, and MAO-B inhibitors—to transiently alleviate motor symptoms such as tremor, rigidity, and bradykinesia. While these regimens provide short-term symptomatic relief, they fail to halt neurodegeneration or modify disease progression. Moreover, long-term use is plagued by diminishing efficacy, motor fluctuations (eg, "wearing-off" phenomena), and adverse effects including dyskinesias, psychiatric disturbances, and impulse control disorders. These limitations highlight the unmet need for disease-modifying therapies capable of targeting PD's multifactorial pathophysiology.[9] As such, individualized treatment protocols tailored to specific symptoms are often necessary.

As an integral component of traditional Chinese Medicine (TCM), acupuncture has safeguarded the health of Chinese over 3000 years, rooted in naturalistic theories compatible with Confucianism and Taoism.[10] Over millennia, acupuncture has evolved into various forms—electroacupuncture (EA), scalp acupuncture, auricular acupuncture, and others. These modern adaptations integrate technological advancements while retaining core principles of traditional meridian theory.[11,12] Among complementary therapies for PD, acupuncture emerges as a particularly compelling intervention due to its multifaceted therapeutic potential. Preclinical studies have demonstrated that acupuncture may exert neuroprotective effects. Clinically, accumulating evidence from RCTs and meta-analyses suggests that acupuncture can significantly improve motor symptoms (eg, bradykinesia, tremor) and non-motor symptoms (eg, bowel movements, sleep disturbances, anxiety).[13–15] Furthermore, its favorable safety profile and minimal side effects enhance its suitability for long-term PD management. Finally, it is the most widely practiced complementary therapies worldwide. While other therapies have value, acupuncture's merits above make it been focused review.

In this context, we conducted a literature review by retrieving data from PubMed, Web of Science, CNKI, VIP, Wanfang, and CBM to present the available evidence on the efficacy and mechanism of acupuncture in treating PD. While numerous reviews have examined acupuncture for PD, our study addresses critical gaps in the literature. Prior reviews primarily focused on clinical efficacy without integrating mechanistic insights from preclinical studies. Conversely, mechanistic reviews often lacked clinical correlation or failed to address PD-specific pathology. Our work bridges this divide by synthesizing evidence from clinical trials and preclinical studies to establish causality between acupuncture's neuroprotective mechanisms and symptom improvement. This dual clinical-mechanistic approach offers a roadmap for personalized acupuncture therapy in PD.

Search Strategy and Selection Criteria

Eligibility Criteria

This review included clinical studies investigating the effects of acupuncture on patients with PD, regardless of age, gender, disease duration, or concurrent medication. Control interventions included placebo, standard medication, or no treatment. What's more, we additionally searched reference lists of relevant studies including animal experiments, meta-analyses, and literature reviews.

Search Strategy

We systematically searched the following electronic databases in June 2024: PubMed, Web of Science, CNKI, VIP, Wanfang and CBM. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to PD including "Parkinson's disease", "PD", "Parkinsonism", "idiopathic Parkinson's", "帕金森病", "震颤麻痹" and Acupuncture including "acupuncture", "electroacupuncture", "manual acupuncture", "needling", "acupuncture therapy" (including proprietary techniques where applicable), "针灸" and "针刺". Language restrictions (English/Chinese) were applied based on database compatibility. Priority was given to studies published within the last five years (2019–2024) to emphasize current evidence, though older seminal studies were not excluded.

Study Selection and Data Extraction

Two independent reviewers sequentially screened titles and abstracts to identify potentially eligible studies before assessing full texts for final inclusion, during which data extraction encompassed patient demographics (including age, gender, and PD severity/duration), intervention details (covering acupuncture type, stimulation parameters, and treatment frequency/duration), control group characteristics (whether placebo, medication, or no treatment), and outcome measures (spanning motor/non-motor symptoms, quality of life, and biomarkers), with all studies being classified as either clinical (involving human subjects) or preclinical (using animal/cell models) to enable separate analysis of clinical outcomes (such as symptom improvement) and mechanistic insights (like pathway modulation) for maintaining methodological rigor.

Causes of PD

The multifaceted causes of PD can be broadly categorized into genetic and non-genetic factors. The significance of genetics in PD is emphasized by the elevated risk associated with a family history of PD or tremor.[16] As genetic techniques and population studies, including genome-wide association studies (GWAS), have advanced, over 20 monogenic forms of PD have been identified, and more than 100 loci have been established as risk factors for developing PD.[17,18]

Among the non-genetic factors, age, gender, and various environmental exposures, including toxins,[19] pesticides,[20] lifestyle habits, and head injuries[21] play pivotal roles. Age is a primary risk factor for PD, yet the nature of this increase—whether it is linear or exponential—remains ambiguous. With the global aging-population and extended life-expectancy, the prevalence of PD is expected to rise steadily, representing a significant public health concern.[22] Gender also significantly influences the etiology and pathogenesis of PD. The incidence, prevalence, and mortality rates of PD are nearly 1.4 times higher in males compared to females, though this gender disparity diminishes after the age of 75. This ratio has remained relatively stable over the past two to three decades,[23] possibly due to the protective effects of estrogen.

In terms of environmental factors, a recent meta-analysis examining 30 potential exposure factors identified 11 environmental exposures that significantly influence the risk of PD.[16] The discovery of neurotoxic effects in a metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which metabolizes into a pro-parkinsonian molecule resembling the herbicide paraquat, has given rise to the hypothesis that exposure to pesticides and other environmental chemicals can mimic the clinical manifestations of PD.[19] This hypothesis is substantiated by research in France, affirming a positive correlation between pesticide exposure (estimated via occupational exposure matrices) and an increased risk of PD, although the dose-response relationship remains unconfirmed.[24]

Another recognized risk factor is prior head injury. According to multiple studies, the risk of developing PD appears to escalate rapidly following traumatic brain injury (TBI).[25] TBI can damage the blood-brain barrier, promote persistent brain inflammation, increase mitochondrial dysfunction, glutamate release, and the accumulation of alpha-synuclein in the brain, all of which may contribute to the development of PD.[26]

Furthermore, there are considerable risk factors for PD remain poorly documented and controversial. These include early-life factors such as the season of birth, birth weight, and parental age, as well as various infections, including measles (which exhibits an inverse relationship), central nervous system (CNS) infections, hepatitis C, and Helicobacter pylori.[27–31]

The Evolution of Acupuncture Treatments for PD

PD was first medically described approximately 200 years ago. At that time, treatments were quite radical, with the researcher James Parkinson advocating bloodletting or venesection from the neck.[32] Subsequently, substances that could induce skin blisters were applied, and small pieces of cork were implanted into the blisters to induce the release of abscess fluid. Apart from "bloodletting therapy", the French neurobiologist Jean-Martin Charcot, in the late 19th century, proposed several management strategies for PD, including rest, stress reduction, and the use of rocking chairs to rhythmically alleviate tremors.[33]

In China, dating back to thousand years ago, the *Huangdi Neijing*, an ancient Chinese medical classic, recorded a disease similar to PD, referring to it as a tremor syndrome in the text. Zhang Zihe from the Jin Dynasty documented a case of "wind convulsion" in his work *Ru Men Shi Qin*, which is potentially the world's first recorded case of PD. For a long time, complementary and alternative medicine (CAM) has demonstrated promising therapeutic effects in the treatment of PD. Despite the relatively late start of experimental research on TCM, CAM remains a relatively popular option for PD in Asian countries, due to its significant therapeutic advantages. Indeed, over one-third of PD patients in the United States (40%) and the United Kingdom (38.7%) have utilized at least one form of CAM for PD treatment, with 7% to 10% specifically opting for acupuncture.[31] Remarkably, after treatment, 70–80% of patients reported marked improvements in subjective symptoms, various motor scores, and enhancements in sleep quality and mood, without any adverse side effects observed.[34] In addition to traditional acupuncture, electroacupuncture (EA), laser acupuncture (LA) and transcutaneous electrical acupoint stimulation (TEAS), which have been evolved based on traditional acupuncture in recent years, have also achieved satisfactory efficacy in the treatment of PD.[35] As PD patients continues to escalate, research into the potential benefits of acupuncture is witnessing a significant proliferation. Two years ago, through data analysis, we delved into the rules of selecting acupoints for the treatment of PD and identified the top ten most frequently used acupoints: Fengchi (GV20), Hegu (LI4), Taichong (LR3), Baihui (GV20), Quchi (LI11), Zusanli (ST36), Wangu (GB12), Yanglingquan (GB34), Tianzhu (BL10), and Taixi (KI3) (see Table 1 for acupoints locations). Commonly used meridians include the Foot Shaoyang Gallbladder Meridian and the Governor Vessel Meridian, with frequent acupoint combinations being LR3-LI4, LI4-GV20-LR3 et al.[36] The selection of acupoints can also be tailored based on varying TCM patterns, providing valuable clinical guidance.

Numerous meta-analyses on the efficacy and safety of acupuncture in PD have been published. Just this year, Anxin Zhang et al conducted a meta-analysis evaluating the impact of acupuncture on neuropsychiatric symptoms in PD

Table 1 The Location and Innervation of Basic Acupoints for PD

Acupoint	Code	Location	Innervation
Taichong	LR3	Located between the first and second metatarsal bones, positioned just below the head (caput) of the metatarsal	S2–3
Taixi	KI3	In depression between tip of medial malleolus and tendocalcaneous	S2-3
Zusanli	ST36	3 cun inferior to ST35, with a distance of approximately one finger-breadth from the anterior border of the tibia, situated between the fibula and tibia.	L4-5, S1-2
Baihui	DU20	Located atop the head, 5 cun above the posterior hairline, approximately centered along the line connecting the tips of both auricles (outer ears)	C2–3
Fengchi	GB20	Positioned on the head, aligned horizontally with the superior margin of the external occipital protuberance	C2–3
Hegu	LI4	Situated on the back of the hand, located radially from the midpoint of the second metacarpal bone	C5-T1
Quchi	LI11	Located on the outer side of the elbow, precisely at the midpoint of the imaginary line connecting LU5 with the lateral epicondyle of the humerus bone	C5-C8, T1
Wangu	GB12	In the anterior region of the neck, in the depression posteroinferior to the mastoid process	C2–3
Yanglingquan	GB 34	Positioned on the fibular side of the leg, within a depression located anteriorly and distally to the head of the fibula bone	L4-5, S1-2
Tianzhu	BL10	Located at the back of the neck, aligned horizontally with the superior edge of the spinous process of the second cervical vertebra, found within a depression lateral of the trapezius muscle	C2–3

patients. Their findings indicate that acupuncture enhances sleep quality, alleviates psychological and behavioral alterations, and overall improves the condition of PD patients.[37] Simultaneously, Suying Lei et al examined the correlation between acupuncture sessions and motor function in PD patients. They discovered that, for treating PD patients with motor symptoms, acupuncture treatment may require achieving a certain dosage to yield optimal therapeutic effects, and excessive acupuncture stimulation may lead to the body developing tolerance.[38] In conclusion, the therapeutic effect of acupuncture for PD is substantial.

Clinical Effect of Acupuncture on PD

PD predominantly affects middle-aged and elderly individuals. Its clinical manifestations can be broadly categorized into two main types: motor and non-motor symptoms.

Motor Symptoms

The motor symptoms of PD predominantly manifest in four categories: bradykinesia, rigidity, resting tremor, and postural instability. Numerous studies have demonstrated that acupuncture significantly mitigates motor symptoms in patients with PD. As early as in 2008, Ren Xiaoming enrolled 80 participants to investigate the efficacy of acupuncture for PD related motor disorders. The study revealed that acupuncture not only potentially enhanced the therapeutic effects of madopar and reduced the required dosage of medication but also achieved a total effective rate of 92% with obvious alleviation of motor disorder in the treatment group, which was significantly higher than that in the control group ($P<0.05$). The study revealed that acupuncture potentially enhanced the therapeutic effects of madopar and reduced the required dosage of medication.[39] Another study conducted by Pingyi Xu et al delved into the curative effect of acupuncture on PD patients experiencing tremor. To maintain blinding, treatments were administered in separate rooms by a single unblinded acupuncturist using bilateral point application with equal numbers of points per session. After treatment, the Unified Parkinson's Disease Rating Scale (UPDRS) II and III scores in the acupuncture group were superior to those the waiting group and sham-acupuncture group. Specifically, in the acupuncture group, the UPDRS III tremor score was notably reduced, while the waiting group was significantly increased, and no significant changes were observed in the sham-acupuncture group.[40] A pilot, assessor-blinded, randomized, controlled, parallel-group trial conducted in Korea assessed acupuncture's impact on gait disturbances in PD patients. The study also analyzed the hemodynamic changes in the cerebral cortex induced by acupuncture. Patients in the acupuncture group exhibited a statistically significant reduction in both cadence and UPDRS scores pertaining to "walking and balance" compared to the controls ($P=0.004$ and $P=0.02$, respectively). Moreover, notable improvements were observed in stride, swing, and single support time ($P=0.006$, $P=0.001$, and $P=0.001$, respectively). Notably, oxyhemoglobin levels in the prefrontal and supplementary motor areas were significantly elevated in the intervention group during treadmill walking, with a noteworthy positive correlation to the duration of the swing phase.[41] Santos MJ et al conducted a randomized, controlled crossover study to qualitatively assess the acute impact of acupuncture on balance and gait in PD patients. Post-treatment, the acupuncture group exhibited statistically significant improvements (all $p<0.05$) in various gait parameters, including gait speed, cadence, support base width, medio-lateral oscillation, left-right step length, stride length (right-right and left-left), duration of left and right support phases, and double support phase, compared to initial assessments. Additionally, there were significant differences in right-left stride length between the acupuncture and sham acupuncture groups. These findings indicate that acupuncture can objectively improve gait performance in PD patients.[42]

Apart from manual acupuncture, multiple acupuncture treatment modalities, including EA, have demonstrated efficacy in the management of PD. A study compared of the efficacy of EA and sham EA in PD patients. After treatment, the EA group exhibited an improvement in balance performance, while the control group showed minimal and non-significant changes ($p>0.29$). Specifically, EA resulted in a 31% reduction in COGML/AP sway, while Ankle/Hip sway experienced a 46% increase under varying conditions, with statistical significance achieved under the dual-task condition ($p=0.02$). Clinical assessments revealed significant overall improvements in activities of daily living (UPDRS part II, 46%) and motor function (UPDRS part III, 40%) ($p<0.01$). Furthermore, there was a marked reduction in specific UPDRS items related to fall risk (67%) and rigidity (48%) ($p<0.02$).[43] A year later, Najafi B et al reached the similar conclusions. Their findings revealed significant improvements in various gait parameters following EA, including gait

speed under single-task habitual walking (STHW), single-task fast walking (STFW), and dual-task fast walking (DTFW), with improvements ranging from 9% to 19% ($p<0.05$). Additionally, stride length during DTFW increased by 9% ($p=0.037$), and midswing speed during STFW improved by 6% ($p=0.033$).[44] Recently, Huangan Wu et al conducted a multi-center RCT to investigate the effectiveness and safety of EA together with conventional pharmacological therapy for managing motor dysfunction in PD. Post-treatment, although the times and steps for the 20-meter walk at week 12, along with the modifications from the baseline in the EA arm, were similar to those in control arm, the EA arm demonstrated a more pronounced reduction in the time required for the 20-meter walk at weeks 16 and 24. These results suggest that EA is a safe and effective treatment option for PD.[13] While acupuncture is commonly used by PD patients, clinical evidence remains mixed. A double-blind randomized pilot study (n=14 Stage II–III PD patients) found no statistically significant improvements in UPDRS motor scores, PDQ-39, or depression scales following acupuncture versus control, though nonsignificant trends toward improved daily living scores were observed.[45] Overall, EA could be a promising alternative treatment for PD patients experiencing balance disturbances.

Scalp acupuncture (SA) represents a distinct acupuncture modality that differs fundamentally from conventional acupuncture through its neuroanatomical basis and standardized stimulation zones.[46] Developed in 1950s China by integrating traditional medicine with Western neuroscience, SA specifically targets the loose areolar tissue between the epicranial aponeurosis and pericranium, modulating corresponding brain regions through cortical localization theory rather than traditional meridians. Pioneered by Dr. Jiao Shunfa in 1970 and later codified by WHO (1984) and Chinese GB/T standards, SA organizes the scalp into discrete functional zones (eg, motor/sensory cortices projections, Yamamoto's points A-E) that enable symptom-specific neuromodulation.[12] Its therapeutic superiority for neurological disorders stems from direct cortical regulation, with key advantages including: (1) precise anatomical targeting based on brain mapping, (2) reproducible protocols standardized by the World Federation of Acupuncture Societies (2006), and (3) broad clinical applicability across ages without specialized equipment.[47] It has shown significant benefits in treating neurological disorders, particularly PD. A study conducted by RuiJie Ma et al aimed to determine whether the integrated approach of Jiao's scalp acupuncture with virtual reality (VR) rehabilitation training yields superior to VR rehabilitation training alone in addressing motor impairments. After 4 weeks of treatment, both groups demonstrated improvements in gait parameters, except for step width in the control group. The timed "up and go" test (TUGT) time decreased, and UPDRS-III scores were reduced significantly ($P<0.01$, $P<0.05$). Specifically, the step distance in the observation group was superior to that in the control group, and the UPDRS-III score in the observation group was lower than in the control group ($P<0.05$). And after 8 weeks, both groups demonstrated further improvements in gait parameters, with a shortened TUGT time and reduced UPDRS-III scores ($P<0.01$). In particular, the step distance and step speed in the observation group were better than those in the control group, the TUGT time in the observation group was shorter, and the UPDRS-III score in the observation group was significantly lower ($P<0.05$, $P<0.01$). This combined approach offers invaluable clinical guidance in treating motor dysfunction related to PD and is regarded as a safe treatment modality.[48] Table 2 summarizes the RCTs mentioned above.

Non-Motor Symptoms

Fatigue

Fatigue, one of the most prevalent non-motor symptoms in PD, is reported as the most disabling symptom by more than half of patients.[49] Current medications, such as stimulants, are often suboptimal or constrained by side effects, resulting in the widespread adoption of alternative medicines, especially acupuncture. Preliminary evidence suggested that acupuncture may reduce fatigue in PD, prompting Louis C.S. Tan and his team to conduct a single-center, randomized, sham-controlled trial to evaluate its effectiveness. Following the treatment, both real- and sham acupuncture groups showed notable improvements in Multidimensional Fatigue Inventory (MFI-GF) and MFI-Total scores at 5 and 9 weeks, without differences between two groups, suggesting that the observed improvements might be due to nonspecific or placebo effects.[50] Following this, Garvan C et al performed a similar study in which 94 PD patients experiencing moderate to severe fatigue were randomly assigned to real and sham acupuncture groups. While acupuncture appeared to alleviate PD-related fatigue, the acupuncture did not yield any greater benefits compared to the sham treatments.[51] Although both RCTs found comparable efficacy between real and sham acupuncture, this does not necessarily imply that

Table 2 The RCTs of Acupuncture for PD-Related Motor Symptom

Ref. ID	Design	Sample Size	Number of Treatments	Interventions	Conclusion	Limitation
39	RCT	80	Once daily, ten sessions constituted a course, totally 2 courses	Acupuncture group: Yangxi (LI5), Yangchi (TE4), Daling (PC7), Yanglao (SI6), LI11, Chize (LU5), Quze (PC3), Shaohai (HT3), Jianliao (TE14), Jianyu (LI15), Jianzhen (SI9), Taixi (KI3), Zhongfeng (LR4), Jiexi (ST41), Yinlingquan (SP9), Yanglingquan (GB34), Weizhong (BL40), Huantiao (GB30), Chengfu (BL36) Western medicine group: madopar	Acupuncture has the capability to enhance the therapeutic effects of madopar while potentially allowing for a reduction in the necessary dosage.	–
40	RCT	41	Without the detailed frequency of treatment	Acupuncture group: levodopa for 12 weeks combined with Baihui (DU20), Fengchi (GB20), and the Chorea-Tremor Controlled Zone. Sham acupuncture arm: levodopa for 12 weeks combined with sham acupuncture. Waiting group: levodopa for 12 weeks	Acupuncture modulated the cerebellum, thalamus, and motor cortex, which are interconnected via cerebello-thalamo-cortical circuit, resulting in the alleviation of PD tremor and an improvement in patients' activities.	Small sample size; without follow-up; not mentioned adverse events; unblinded to the operator about assignment
41	RCT	26	Received therapy twice a week for 4 consecutive weeks.	Only described the approximate location of the acupoints, without the accurate acupoint information.	Acupuncture exhibited a propensity to improve hypometric gait and reorganize the activation patterns within the cerebral cortex.	Small sample size, not blinded to participants and practitioner
42	RCT	7	The intervention lasted 30 min.	Acupuncture group: Shenmen (HT7), HT3, KI3, Fuliu (KI7), Gongsun (SP4), Chengshan (BL57) and Liangqiu (ST34).Sham acupuncture group: the points located 1/2 cun next to or above the true acupoints.	Acupuncture has been shown to objectively enhance gait performance among individuals with PD.	Small sample size, the practitioner was not blinded to the intervention
43	RCT	59	A weekly 30-minute EA treatment administered over a period of three weeks.	EA group: DU20, DU14 (Dazhui), LI4 (Hegu), ST36 (Zusanli), GB34, LR3 (Taichong), KI3 (Taixi), SP6 (Sanyinjiao), BL40 (Weizhong). Sham EA group: insert needles under the skin at non-acupoints surrounding the aforementioned, and apply a minimal intensity stimulation in a comparable manner	EA showcased an enhancement in rigidity and balance, which could potentially serve as a viable alternative therapy for balance impairments in individuals with PD.	Small sample size
44	RCT	15	Three consecutive weeks of once weekly, 30-minute sessions.	EA group: Foot Motor Sensory Area, Balance Area, DU20, GV14, LI4, ST36, GB34, BL40, SP6, KI3, LR3 Sham EA group: insert needles less than 4mm without manipulation, under the skin at non-acupoints surrounding the aforementioned	EA has the potential benefits in enhancing gait among patients with PD.	Small sample size, not be fully objective randomization

(*Continued*)

https://doi.org/10.2147/NDT.S532027

Table 2 (Continued).

Ref. ID	Design	Sample Size	Number of Treatments	Interventions	Conclusion	Limitation
13	RCT	166	Totally 36 sessions, administer 30- minute sessions three times each week for 12 weeks.	Control group: levodopa EA group: levodopa combined with the bilateral connection of Qianding (DU21) to Xuanlu (GB5), Connect Qianshencong (EX-HN1) to Xuanli (GB6), LI11, SP6, LI4, GB34, ST36, KI3 and LR3	The combination of conventional therapy with EA has been found to significantly improve motor function in patients with PD, as compared to conventional treatment alone.	Patients were not blinded leading to suboptimal adherence in sham EA arm.
45	A double blind study	14	Each session lasts 20 minutes, with 1–3 sessions per week over two weeks	EA group: KI3, KI10 (Yingu), BL60 (Kunlun), LR3, ST41, ST36, GB34, bafeng points, MH6, LI4, GV20 Nonacupuncture group: in the arms, legs, and scalp, in areas that did not have any known acupoints	This RCT found no significant benefits of acupuncture over control in PD patients, though minor non-significant improvements were seen in daily function, quality of life, and motor symptoms.	Small sample size, lack of individualization of the treatments
48	RCT	52	Administered once daily, five times per week, for a duration of 8 weeks.	Control group: routine treatment together with VR rehabilitation Observation group: based on control group together with Jiao's scalp acupuncture, including the scalp points at the movement area, balance area and dance tremor control area.	Scalp acupuncture combined with VR rehabilitation was superior to VR rehabilitation alone in enhancing walking ability, gait parameters, and motor function in PD patients.	-

https://doi.org/10.2147/NDTS532027

acupuncture is ineffective for alleviating fatigue. Interestingly, Li J and her team employed transcutaneous electroacupoint stimulation (TEAS), a modality of acupuncture stimulation techniques, to assess its impact on postoperative fatigue (POF) among PD patients undergoing deep brain stimulation (DBS) surgery. The TEAS group showed better outcomes in terms of POF, mini-mental state examination (MMSE), and Quality of Recovery-15 (QoR-15) scores compared to the control group.[52] While several RCTs showed similar effects between real and sham acupuncture, this does not negate acupuncture's potential anti-fatigue benefits. The comparable outcomes may reflect physiological placebo effects from sham procedures, non-individualized point selection diluting specificity. These findings reflect acupuncture's complex mechanisms (both neurophysiological and psychosocial) beyond point specificity.

Constipation

Most PD patients accompanied by gastrointestinal symptoms of varying severity, commonly including constipation, nausea, and dry mouth.[53] It has been demonstrated that acupuncture is both effective and safe in treating PD-related constipation. A RCT suggested that, compared to the sham acupuncture group, the weekly number of complete spontaneous bowel movements (CSBMs) was significantly higher in the acupuncture group ($P<0.001$). Additionally, the improvement in CSBMs in the acupuncture group persisted throughout the follow-up period ($P<0.001$).[54] And the RCT conducted by Huangan Wu et al investigated the therapeutic effects of acupuncture on constipation. From week 4 to week 24, the median number of spontaneous bowel movements per week in the EA group were consistently higher than those in the control group, with all differences being statistically significant.[13] In summary, EA significantly enhanced bowel movements in PD patients. However, another study revealed that post-treatment with EA did not lead to significant improvements in the Bristol Stool Form Scale (BSFS) or the Patient-Associated Constipation and Quality of Life Scale (PAC-QOL).[55]

PD-Related Pain

More than two-thirds of PD patients experience pain, which often stems from motor fluctuations, dystonic muscle contractions, deep visceral pain, and musculoskeletal discomfort.[56] This pain typically emerges in the early stages of PD and can persist for several years prior to clinical diagnosis, significantly impacting the quality of life for those affected.[57] Evidence suggests that acupuncture can, to a certain extent, alleviate pain in PD patients. A study conducted by Wang JJ et al examined the efficacy of acupuncture in managing PD-related pain. Post-treatment results revealed a notable reduction in the total scores on the King's Parkinson's Disease Pain Scale (KPPS) and the UPDRS in the acupuncture group, specifically a 46.2% and a 21.6% decline, respectively. This study has bolstered users' trust in acupuncture as an efficacious and safe analgesic approach for PD-related pain.[58] Anther single-center RCT has evaluated the effectiveness of EA for skeletal muscle pain in PD. The results showed that the KPPS score and visual analog scale (VAS) score in the EA group were significantly lower than those in control group ($P<0.05$). Furthermore, Spearman correlation analysis revealed a positive correlation between KPPS scores and UPDRS III and HAMD scores ($r=0.414$, $P<0.05$; $r=0.576$, $P<0.01$ respectively). These findings suggest that EA can effectively alleviate skeletal muscle pain in PD patients, reduce muscle stiffness, enhance daily living abilities, and alleviate emotional disorders.[59] At present, a randomized trial evaluated fire needling therapy (FNT) in 60 PD patients, revealing significant KPPS reductions versus controls at week 4 (−20.693[−27.619,-13.767], $P<0.001$), week 8 (−44.680[−52.359,-37.000], $P<0.001$), and week 12 (−44.982 [−52.771,-37.193], $P<0.001$), with parallel improvements in VAS, UPDRS-III, and PDQ-39 scores. These consistent results across acupuncture modalities - from traditional needling to specialized FNT - substantiate acupuncture's value in PD pain management while highlighting the need for multicenter validation of FNT's therapeutic potential.[60]

PD-Related Sleepiness

Sleep disorders, frequently encountered as a consequence of disease progression and as adverse effects of anti-Parkinsonian medications, are a prevalent non-motor symptom in PD. Their presence is significantly associated with a more severe clinical phenotype, indicating a more pronounced or challenging disease manifestation.[61,62] A RCT conducted in Brazil rigorously evaluated the influence of acupuncture on sleep disturbances among patients with idiopathic PD. The findings indicated that, in comparison to participants who did not receive intervention, those who underwent acupuncture demonstrated a potential therapeutic advantage in alleviating sleep disturbances.[63] Nowadays, to assess the effectiveness of acupuncture in ameliorating sleep disturbances in PD patients, Zhuang L. et al randomized 78

participants into real- and sham acupuncture groups. In both groups, a significant increase in Parkinson Disease Sleep Scale (PDSS) scores from baseline was observed (29.65 [95% CI, 24.65–34.65], P<0.001; 10.47 [95% CI, 5.35–15.60], P<0.001). Remarkably, the acupuncture group exhibited a significantly more pronounced improvement in PDSS scores compared to the sham acupuncture group, both immediately after treatment and during the follow-up period (19.75 [95% CI, 11.02–28.49], P<0.001; 20.24 [95% CI, 11.51–28.98], P<0.001). These findings underscore the benefits of acupuncture in improving sleep quality among PD patients, with therapeutic gains persisting for at least 4 weeks post-treatment.[15] Apart from these findings, a recent RCT enrolled 60 PD patients with insomnia revealed that acupuncture yielded superior outcomes compared to sham acupuncture, including significantly better PDSS scores (21.4-point difference [95% CI, 15.6–27.2] sustained through week 16), greater Pittsburgh Sleep Quality Index reductions (TA: 8.9 points [95% CI, 3.6–14.2] vs SA: 10.8 points [95% CI, 4.3–17.3] at week 4), along with improved sleep latency, duration and efficiency, collectively suggesting that acupuncture may offer a safe and effective approach for managing PD-related sleep disturbances, though further research is warranted to fully establish its clinical utility.[64]

Neuropsychiatric Disorder

PD is now recognized conceptualized as a complex neuropsychiatric disorder, and in many cases, neuropsychiatric symptoms such as depression and anxiety often occurring alongside the disease. These symptoms tend to have similar correlations and significantly impact the course of the illness.[65] Depression, a multifaceted condition, follows a bimodal progression in PD. Reports indicate that the incidence of depression among PD patients ranges from approximately 20–30%, and in some cases, it may even precede the onset of motor symptoms.[66] A retrospective analysis of 48,981 individuals newly diagnosed with depression (2000–2012) from Taiwan's National Health Insurance Research Database (NHIRD) compared PD incidence between those receiving acupuncture and matched non-acupuncture controls. After adjusting for factors such as age, sex, insurance premiums, and other relevant variables, acupuncture was associated with a 61% lower risk of PD development [adjusted hazard ratio (aHR) = 0.39, 95% CI=0.31–0.49], compared to those who did not receive acupuncture. Kaplan–Meier analysis confirmed a significantly lower cumulative PD incidence in the acupuncture cohort (Log rank test, p<0.001). These findings indicate that acupuncture is associated with a reduced risk of PD in patients with depression.[67] A RCT also explored the therapeutic effect of sham- and real acupuncture on PD patients comorbid with anxiety. Upon treatment completion, the variation of Hamilton Anxiety Scale (HAM-A) scores showed no statistically significant difference between two groups. These findings suggest that, in this particular study, acupuncture did not outperform sham acupuncture in alleviating anxiety in PD patients. However, upon completion of the follow-up, the real acupuncture group achieved a 7.03-point greater (95% CI, 6.18 to 7.88; P<0.001) decrease in HAM-A score compared with the sham group. Throughout the study, four mild adverse events were recorded. These findings underscore the potential of acupuncture as an effective treatment for anxiety in PD patients, suggesting it may improve their overall well-being and quality of life.[14] Table 3 summarizes the detail of PD-related non-motor symptoms treated with acupuncture.

Mechanism of Acupuncture on PD

PD is neuropathologically defined by the progressive degeneration and eventual loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), a process pathologically marked by the accumulation of α-synuclein aggregates and the formation of Lewy bodies.[68] This neurodegeneration triggers a critical depletion of striatal dopamine (DA), disrupting the delicate neurotransmitter equilibrium within the basal ganglia-thalamocortical circuitry. The resultant dopaminergic deficit underlies the cardinal motor symptoms of PD, including bradykinesia, resting tremor, rigidity, and postural instability.[69] Furthermore, widespread dysregulation of multiple neurotransmitter systems—including serotonin (5-HT), norepinephrine (NE), gamma-aminobutyric acid (GABA), and glutamate (Glu)—in both central and peripheral neural networks contributes to the heterogeneous non-motor manifestations of PD, such as autonomic dysfunction, neuropsychiatric disturbances, sleep architecture abnormalities, and gastrointestinal dysmotility.[70] Emerging clinical evidence highlights acupuncture as a promising neuromodulatory intervention for PD management. Mechanistically, preclinical studies demonstrate that acupuncture exerts multifaceted neuroprotective effects: (1) inhibiting α-syn fibrillization and propagation in dopaminergic neurons, (2) attenuating mitochondrial dysfunction, oxidative stress, and caspase-dependent apoptosis pathways, (3) modulating DA-associated neuroinflammatory responses through microglial

Table 3 The RCTs of Acupuncture for PD-Related Non-Motor Symptom

Ref. ID	Design	Sample Size	Number of Treatments	Interventions	Conclusion	Limitation
50	RCT	40	2 sessions weekly, with 3 days apart between sessions at least, for 5 weeks and 10 sessions in total.	Sham acupuncture group: PC6 (Neiguan), LI4, ST36, SP6, KI3, and Qihai (CV6). Acupuncture group: the same protocol as sham acupuncture group	Acupuncture has proven to be a safe and efficacious treatment for alleviating fatigue in patients with PD.	Small sample size
51	RCT	94	Twice a week, at least 1 day apart, for 6 weeks	Sham acupuncture group: GV20, ShenTing (GV24), CV6, Shousanli (LI10), HT7, ST36, SP6. Acupuncture group: the same protocol as sham acupuncture group	Acupuncture may alleviate PD- related fatigue, but real acupuncture does not confer any additional benefit over sham or placebo treatment.	Lack a wait-list, usual care, or prospective control arm
52	RCT	78	One session	TEAS group: ST36 and SP6 Control group: ST36 and SP6	ITEAS mitigated the severity of POF, decreased the intraoperative anesthetic requirements and facilitated PD-patients recovery.	Small sample size, a single center, lacks a group receiving only standard care
54	RCT	78	Three times a week over a 4-week period totally 12 sessions	Sham acupuncture group: Sishenzhen consists of four acupoints, namely Qianding (GV21), Houding (GV19), and next to GV20 1.5 cun bilateral, GV29 (Yintang), ST25 (Tianshu), GV24, CV4 (Guanyuan), and ST3 (Shangjuxu) Manual acupuncture group: the same protocol	Acupuncture was effective and safe in treating PD-related constipation, and the treatment effect persisted for up to 4 weeks.	The effect of acupuncture on levodopa dose could not be observed due to the short period
13	RCT	166	30-minute session three times per week for a duration of 12 weeks, a total of 36 sessions.	Control group: levodopa EA group: levodopa combined with bilateral connection of DU21 to GB5, connect EX-HN1 to GB6, LI11, SP6, LI4, GB34, ST36, KI3 and LR3	EA significantly enhanced bowel movements in PD patients	Not blinded lead to suboptimal adherence in sham EA arm.
55	RCT	30	Twice a week for 30 min based on drug treatment for 8 weeks.	Acupuncture group: DU20, GB20, CV4, Zhongwan (RN12), ST25, ST36, SP6, IL4, Fenglong (ST40), and LR3 Control group: conventional drug	EA may be a complementary and alternative vehicle for PD patients.	Small sample size
58	RCT	16	Totally 16 sessions	Acupuncture group: GV20, Shenguan, GB34. Control group: received an analgesic agent	Acupuncture could relieve pain in PD patients.	Small sample size, without sham group
59	RCT	60	A total of 20 sessions	Acupuncture group: DU20, CV6, Lieque (LU7), Tinggong (SI19). Upper pain add Jianyu (LI15), Quchi (LI11), Lower pain add Xuehai (SP10), ST36. Control group: the same protocol with the Park needle	EA can improve skeletal muscle pain in PD patients, reduce their muscle hardness, improve the daily life ability.	Small sample size, without follow-up
60	RCT	60	Without detailed information	Fire needling group: GV16 (Fengfu), GB20, UB10 (Tianzhu), GB12 (Wangu), and ashi point Control group: usual care	Fire needling therapy is effective and safe in managing PD-related chronic pain.	Without sham control, not blinded

(*Continued*)

Table 3 (Continued).

Ref. ID	Design	Sample Size	Number of Treatments	Interventions	Conclusion	Limitation
63	RCT	22	8 sections (once a week)	Acupuncture group: Waiguan (TE5), LR3, SP6, LI4, HT7, PC6, LI11, GB20 Control group: no intervention.	This research highlighted a potential therapeutic benefit of acupuncture in addressing sleep disturbances experienced by PD patients.	Heterogeneous groups and differences in patient age and stage of PD
15	RCT	78	Three times weekly (specifically on Monday, Wednesday, and Friday) for a duration of four consecutive weeks.	Acupuncture group: Sishenzhen, GV24, GV29, LI4, LR3, SP6, HT7, ST36, Shenmai (BL62), and Zhaohai (KI6) Sham acupuncture group: the same protocol	Acupuncture has been found to be effective in enhancing sleep quality among individuals with PD, with the therapeutic benefits extending for up to four weeks post-treatment.	Unblinded to acupuncturists; limited follow-up period; single-center
64	RCT	60	A duration of 30 min per session, 3 times a week, totaling 12 sessions	True acupuncture group: BL62, KI6, PC7, HT7, and Jiaji (EX-B2) Sham acupuncture group: the same acupoints as acupuncture group	Acupuncture may enhance the management of patients with PD-related insomnia.	Insufficient duration of treatment;

https://doi.org/10.2147/NDT.S532027

polarization, and (4) restoring functional connectivity in basal ganglia-thalamocortical circuits. These synergistic mechanisms collectively contribute to acupuncture's therapeutic efficacy in ameliorating both motor and non-motor symptoms of PD, as summarized in Figure 1A and B, which illustrate the interplay between PD pathology progression and acupuncture-mediated neuroprotection.

α-Synuclein Aggregation

The pathogenesis of PD involves the progressive misfolding and aggregation of soluble α-synuclein monomers into insoluble fibrillary Lewy bodies, a hallmark neuropathological feature.[71] In the substantia nigra (SN) and striatum (ST), this aberrant α-synuclein accumulation exacerbates dopaminergic neuron degeneration through mitochondrial dysfunction, oxidative stress amplification, and sustained neuroinflammatory cascades. Emerging evidence suggests that acupuncture exerts neuroprotective effects by targeting α-synuclein dynamics. Mechanistically, serum/glucocorticoid-regulated kinase 1 (SGK1)—a serine/threonine kinase implicated in α-syn regulation—has been identified as a key mediator. Yeo and Lim demonstrated that acupuncture at GB34 and LR3 upregulated SGK1 expression, concurrently suppressing pathological α-synuclein accumulation.[72] Complementary in vitro experiments using SGK1 siRNA knockdown in SH-SY5Y dopaminergic cells revealed a direct inverse relationship between SGK1 levels and α-synuclein expression, confirming SGK1's regulatory role in α-synuclein homeostasis. Crucially, phosphorylation of α-syn at serine 129 (pSer129-α-syn) potentiates its neurotoxic oligomerization. Preclinical studies reveal that acupuncture not only reduces total α-synuclein burden in SN and ST but also specifically attenuates pSer129-α-synuclein isoforms (p-α-synuclein 32 and p-α-synuclein 16), thereby mitigating neurotoxic sequelae in surviving dopaminergic neurons.[73] This dual modulation of α-synuclein aggregation and post-translational modification positions acupuncture as a multifaceted inhibitor of synucleinopathy progression. A critical neuroprotective mechanism of acupuncture involves the restoration of autophagy-lysosomal function to degrade pathogenic α-synuclein aggregates. Tian et al demonstrated that four-day acupuncture treatment at GB34 enhanced autophagic flux in SNpc neurons, evidenced by a 40% reduction in LC3-II (autophagosome marker) and 20% decrease in LAMP1 (lysosomal marker), concomitant with >50% clearance of nigral α-synuclein deposits.[74] Strikingly, this effect occurred independently of canonical mTOR signaling, as upstream regulators (p-mTOR, p-p70S6K, ULK1) remained unaltered. Instead, acupuncture appears to directly stabilize lysosomal integrity, bypassing mTOR-mediated autophagy suppression. This mTOR-independent action holds therapeutic significance. While mTOR inhibitors like rapamycin enhance autophagy, their clinical utility in PD is limited by adverse effects, including dyslipidemia, renal impairment, and immunosuppression.[75] In contrast, acupuncture achieves comparable autophagy potentiation without disrupting mTOR-regulated physiological processes. Notably, mTOR activation typically suppresses autophagy via phosphorylation of downstream effectors (p-p70S6K and p-4E-BP1), creating a barrier to pharmacological intervention.[76] Acupuncture's ability to circumvent this regulatory checkpoint highlights its unique advantage as a low-risk adjunctive therapy for PD.

Apoptosis

In PD, dopaminergic neurons in the SN undergo programmed cell death, leaving apoptotic bodies as pathological remnants in brain tissues.[77] Acupuncture counteracts this neurodegeneration by targeting intrinsic and extrinsic apoptotic pathways. MA and acupoint injection at ST36 similarly modulate mitochondrial apoptosis regulators, suppressing pro-apoptotic Bax and cytochrome C release while upregulating anti-apoptotic Bcl-2.[78] A systems-level study by Park et al[79] identified the p53 signaling network as central to acupuncture's neuroprotection: 52.6% (40/76) of acupuncture-responsive differentially expressed genes were functionally linked to p53, and conditional p53 knockdown in midbrain dopaminergic neurons abolished acupuncture's therapeutic effects. Mechanistic divergences emerge across stimulation modalities: While bee venom acupuncture (BVA) at GB34 rescues dopaminergic neurons by inhibiting c-Jun N-terminal kinase (JNK)-mediated c-Jun activation in MPTP models,[80] traditional MA at the same acupoint shows no significant modulation of phosphorylated c-Jun (p-c-Jun) levels.[81] This discrepancy underscores the necessity for comparative studies elucidating how acupuncture techniques differentially regulate JNK signaling cascades. The neurotrophic hypothesis posits brain-derived neurotrophic factor (BDNF) as a critical mediator of dopaminergic neuron survival and plasticity.[82] Preclinical evidence demonstrates that high-frequency EA at GV14 and GV20 upregulates midbrain

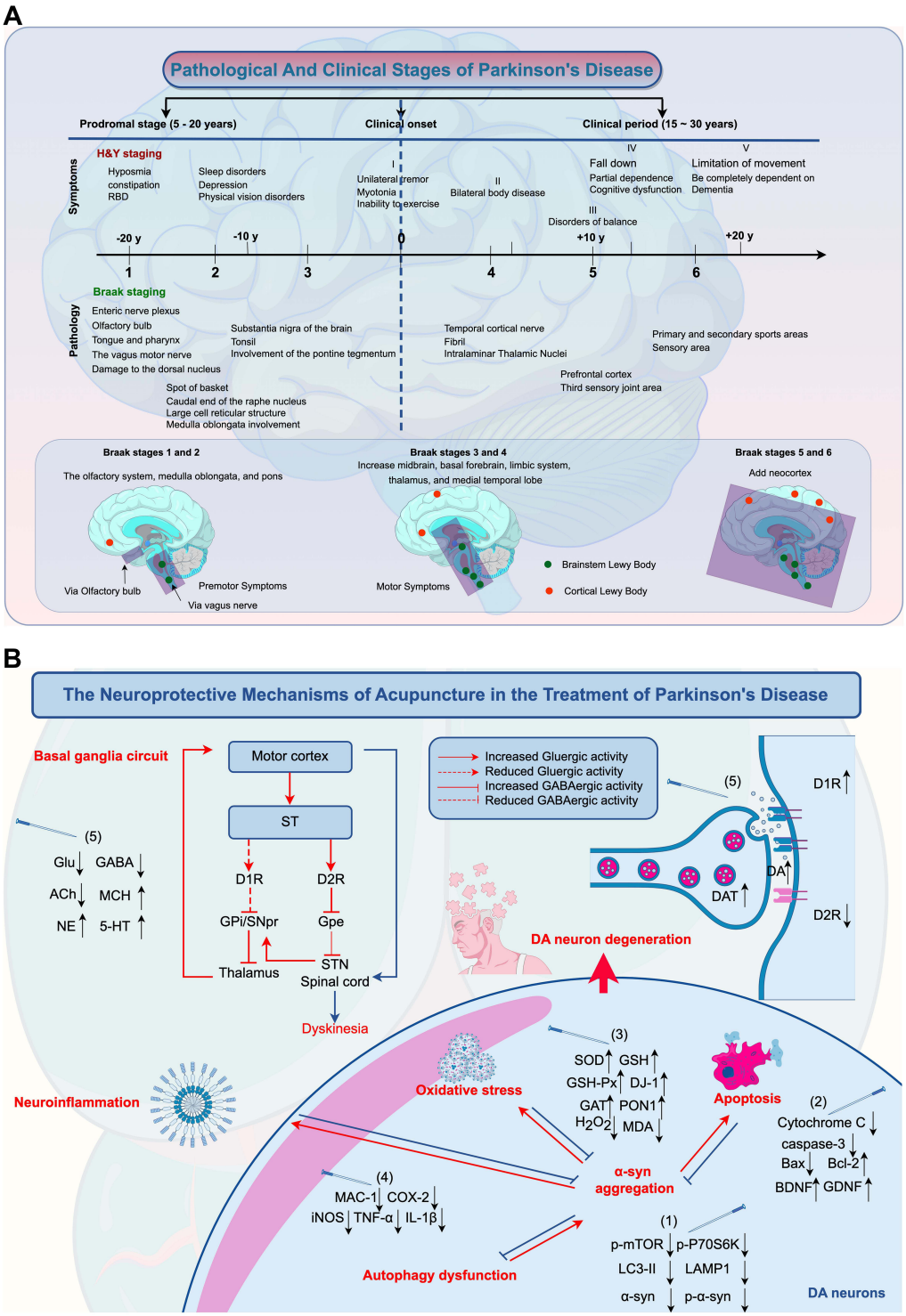

Figure 1 L Clinical and basic research of PD. (**A**) PD was divided into five stages, namely Hoehn-Yahr scale: Stage 0: Asymptomatic. Stage (I) Unilateral limb symptoms (tremor, rigidity, bradykinesia) with minimal functional impairment. Stage II: resting tremor, myotonia and bradykinesia may occur in two limbs, but normal posture can still be maintained. Stage lll: Some degree of active limitation, mild or moderate dysfunction, but can still live independently. Stage IV: Difficult living, but can barely stand and walk without support. Stage (V) Unable to stand, without assistance, limited mobility. According to the main composition of Louis body α-synuclein difference of deposition area and the time of the PD pathogenesis and sequence in PD pathological changes can be divided into 6, the onset of PD from medulla oblongalta to the development of the cortex's rising. The pathological changes of PD start from the olfactory bulb and the dorsal nucleus of the vagus nerve, and progress upward, gradually involving the raphe nucleus, locus coeruleus, and giant cell reticular nucleus, and then involving the midbrain, especially the substantia nigra. At this time, related motor symptoms often appear. Later, the basal forebrain, medial temporal lobe, and neocorcortex are involved, which are divided into 1–6 stages according to the course of the disease. (**B**) The neuroprotective mechanisms of acupuncture in the treatment of Parkinson's disease. The pathological activities associated with PD include α-syn aggregation, oxidative stress, apoptosis, neuroinflammation, and the disbalance of basal ganglia circuit (red). The key molecules (blue) in the above events are regulated by acupuncture to display neuroprotective effect in PD brain.

BDNF levels, preventing ventral tegmental dopaminergic degeneration and fostering neuronal regeneration.[83] Frequency-dependent effects are evident: 2 Hz EA elevates glial cell line-derived neurotrophic factor (GDNF) mRNA bilaterally in the globus pallidus, whereas 100 Hz EA additionally increases GDNF expression in the substantia nigra pars reticulata.[84] These frequency-specific responses suggest EA modulates retrograde GDNF transport from basal ganglia nuclei to the SN, rebalancing cortico-striatal circuitry in PD models.[85] Tyrosine kinase receptor B (TrkB), a high-affinity receptor for BDNF, plays a crucial role in neuronal differentiation and survival.[86] Acupuncture at GB34 and LR3 has been shown to increase TrkB expression in the damaged substantia nigra of 6-hydroxydopamine (6-OHDA)-induced PD rats.[87] The neuroprotective effects of EA appear to be mediated through TrkB, as the TrkB inhibitor K252A abolishes these effects. Furthermore, EA may reverse the imbalance between TrkB FL and TrkB T1, leading to the upregulation of p-Akt, p-ERK1/2, and BDNF.[88] Specifically, 50 Hz EA at GB34 and LR3 has been shown to increase BDNF and downstream p-Akt levels.[89] When combined with KD5040, acupuncture at GB34 downregulated pIκBα while upregulating pAkt, pGSK3β, pERK, pCREB, and BDNF, significantly improving motor function.[90] Beyond apoptosis regulation, acupuncture stimulates endogenous repair mechanisms. Increased 5-bromo-2′-deoxyuridine (BrdU)-positive cells in the subventricular zone indicate restored neurogenic potential, suggesting a novel pathway for dopaminergic circuit reconstruction in PD.[91] This proliferative effect, coupled with BDNF/GDNF-mediated synaptic plasticity, positions acupuncture as a multimodal intervention capable of both neuroprotection and neural network rehabilitation.

Oxidative Stress

The pathological accumulation of free radicals induces lipid peroxidation chain reactions, generating sustained oxidative stress during protein synthesis in dopaminergic (DA) neurons. This redox imbalance disrupts membrane phospholipid architecture through peroxidative degradation, ultimately triggering apoptotic cascades in DA neurons.[92] Emerging evidence suggests acupuncture therapy may exert neuroprotection via multi-target modulation of endogenous antioxidant systems. Preclinical studies demonstrate that MA at GB34, LR3, ST36, and SP10 significantly enhances enzymatic antioxidants including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and reduced glutathione (GSH), while reducing lipid peroxidation marker malondialdehyde (MDA) in PD models. These biochemical improvements correlate with enhanced motor coordination in rotarod testing.[93] Notably, diverse acupuncture modalities share convergent antioxidant effects: EA at ST36 and SP6 elevates striatal GSH and SOD while suppressing hydrogen peroxide (H2O2) and MDA levels;[94] blood-letting vacuum aspiration (BVA) at GB34 enhances paraoxonase-1 activity and GSH recycling capacity alongside MDA reduction.[95] Mechanistically, the redox-sensitive chaperone protein DJ-1 emerges as a critical mediator. DJ-1 executes neuroprotection through dual mechanisms: 1) Direct ROS scavenging via its deglycase activity, and 2) Inhibition of apoptosis signal-regulating kinase 1 (ASK1) through nuclear sequestration of Daxx adaptor protein.[96,97] Experimental data suggest acupuncture at GB34 upregulates DJ-1 expression while coordinately activating striatal SOD and catalase (CAT), thereby establishing a synergistic antioxidant network.[98,99] Collectively, these findings position acupuncture as a regulator of redox homeostasis, counteracting oxidative damage to preserve DA neuronal integrity.

Neuroinflammation

As the primary immunocompetent cells of the CNS, microglia critically drive neuroinflammatory cascades in PD pathogenesis.[100] Degenerating dopaminergic neurons release damage-associated molecular patterns (DAMPs), polarizing microglia toward a pro-inflammatory M1 phenotype. This activation triggers excessive production of ROS and pro-inflammatory cytokines—including TNF-α, IL-1β, IL-6, and IL-12—culminating in oxidative stress amplification and dopaminergic apoptosis.[101] Acupuncture at GB34 and LR3 demonstrates potent anti-inflammatory effects in MPTP-induced PD models, suppressing microglial activation markers (MAC-1) while downregulating inflammatory mediators COX-2 and iNOS.[102] These molecular changes correlate with functional recovery: striatal dopamine levels rise from 46% to 78% within 7 days of treatment, underscoring acupuncture's dual role in mitigating glial hyperactivity and preserving nigrostriatal integrity. Emerging evidence positions the brain-gut axis as a pivotal mediator of PD pathophysiology. Chronic gut dysbiosis in PD models promotes α-synuclein overexpression, neuroinflammation via microglial priming, and gastrointestinal comorbidities like constipation.[103] Acupuncture exerts systemic anti-inflammatory effects by rebalancing gut microbiota composition. Jang et al[78] identified acupuncture-induced modulation of key genera—

Butyricimonas, Holdemania, Frisingicoccus, Gracilibacter, Phocea, and Aestuariispira—whose abundance correlates with both motor improvement and anxiety reduction. PICRUSt-predicted metagenomic analyses further reveal acupuncture's capacity to restore glutathione metabolism and methane cycling, pathways critical for PD-associated redox homeostasis. Mechanistically, acupuncture at ST36 mimics these effects through vagal modulation, reducing colonic iNOS/COX-2 expression and enhancing locomotor capacity in MPTP mice.[104] The intervention concurrently increases SN/ST dopaminergic fibers, suppresses astrocytic (GFAP) and microglial (Iba1) activation markers, and reverses Bax/Bcl-2 apoptotic imbalance, demonstrating multimodal neuroprotection. Nigral iron accumulation, a hallmark of early PD, synergizes with gut-derived inflammation to exacerbate neurodegeneration. Acupuncture at CV12 (Zhongwan), ST25, and CV4 targets this pathophysiology by: reducing duodenal α-synuclein aggregates and systemic IL-1β/TNF-α levels; normalizing iron transport via downregulation of duodenal DMT1 (iron importer) and upregulation of FPN1 (iron exporter); Attenuating iron deposition in both duodenum and substantia nigra.[105] This tripartite mechanism not only alleviates gastrointestinal symptoms but also disrupts the "gut inflammation-iron dysregulation-α-synuclein pathology" axis,[106] offering a novel therapeutic strategy for PD-related motor dysfunction.

Preclinical studies mainly explore the mechanism of acupuncture for PD based on animal models, but there is a significant gap in its clinical translation. On the one hand, it is difficult for animal models to fully simulate the complex pathological features of human PD (such as non-motor symptoms and long-term disease progression), and the regulatory mechanisms of acupuncture on neural circuits may be intrinsically different between rodents and humans. On the other hand, the individual heterogeneity of clinical patients (including key variables such as disease stage, acupoint selection and stimulation parameters) cannot be accurately reproduced by standardized animal experiments, which leads to the discrepancy between the prediction of therapeutic effect in basic research and the clinical reality. To bridge this translational gap, it is necessary to combine new research tools such as multimodal imaging technology and organoid models, and establish a cross-species research system that is closer to the characteristics of human diseases.

Summary

PD constitutes a critical component of global health literacy, particularly in aging populations. In China, the prevalence of PD among individuals aged ≥65 years is 1,700 per 100,000, aligning closely with epidemiological patterns observed in Europe and North America. Incidence escalates with advancing age, exhibiting a slight male predominance. Against the backdrop of China's rapidly aging demographic, PD imposes a dual burden: deteriorating quality of life for patients and escalating socioeconomic costs for families and healthcare systems. This underscores the urgency of addressing PD-related biopsychosocial challenges, including modifiable lifestyle risk factors and comorbidities.

TCM particularly acupuncture, is emerging as a globally recognized adjunctive therapy for PD, which offers a favorable safety profile and potential for sustainable, holistic benefits, particularly as an adjunctive therapy. Clinical studies validate its ability to ameliorate both motor deficits (tremor, rigidity, postural instability) and non-motor symptoms (constipation, depression, sleep disturbances) through multifactorial mechanisms: neurochemical modulation: Enhancing striatal dopamine release and synaptic plasticity; neuroprotection: Mitigating oxidative stress, α-synuclein aggregation, and mitochondrial dysfunction; systemic regulation: Restoring gut-brain axis homeostasis and reducing neuroinflammation.

While robust evidence from RCTs supports acupuncture's efficacy and safety in PD—with adverse events typically mild and self-limiting (eg, transient bruising)—critical limitations remain, including small sample sizes, methodological flaws, and heterogeneity in protocols (eg, needling depth, acupoint selection, and stimulation parameters). What's more, RCTs documented various blinding methods (including non-penetrating sham needles and placebo needling devices), current sham approaches like non-acupoint needling or superficial penetration may not be fully inert due to physiological effects of skin stimulation. This fundamental limitation complicates efficacy attribution in PD trials, where substantial placebo responses are common, making it difficult to distinguish specific therapeutic effects from enhanced non-specific responses. Although recent efforts like the STRICTA guidelines aim to standardize reporting, further work is needed to establish consensus on optimal protocols tailored to PD subtypes. Additionally, while preclinical studies suggest neuroprotective mechanisms, these require validation through large-scale, well-designed clinical trials with longitudinal follow-up to assess disease-modifying potential. Future research on acupuncture for PD should concentrate on three

pivotal areas: first, conducting multicenter large-scale clinical trials using standardized STRICTA criteria to establish optimized protocols for different PD subtypes; concurrently, it is essential to investigate the synergistic mechanisms between acupuncture and conventional medications/rehabilitation therapies to develop personalized integrated treatment strategies based on symptom profiles and disease stages. These studies must specifically address current methodological limitations in the evidence base, including inadequate sample sizes and protocol heterogeneity, while validating clinical trial findings through real-world studies to provide more reliable evidence for clinical practice.[107]

Given its non-invasive nature, cost-effectiveness, and potential to complement conventional therapies, acupuncture holds promise as part of holistic PD management - though these potential benefits need further confirmation through high-quality trials - with broader adoption ultimately hinging on resolving these evidence and implementation gaps.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Young Chinese medicine research project (ZHY2023-207), The Special project of popularization of Traditional Chinese Medicine Classics in Heilongjiang Province (ZYW2024-118).

Disclosure

The authors report no conflicts of interest in this work.

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