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Treatment of Depression in Parkinson's Disease: Pathological Mechanisms and Clinical Practice

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Abstract:

Depression, a non-motor symptom, frequently occurs alongside Parkinson's disease (PD), which is a prevalent neurodegenerative disorder among middle-aged and elderly individuals. Its treatment necessitates balancing the alleviation of depressive symptoms against the risk of worsening motor symptoms. Conventional antidepressants exhibit limited efficacy, are prone to inducing adverse reactions, and further exacerbate issues such as diminished patient quality of life and increased caregiving burden. In-depth exploration of the pathological mechanisms of depression in Parkinson's Disease (PDD) and optimization of diagnosis and treatment strategies are of great significance. This article reviews the pathological mechanisms (abnormal neurotransmission, inflammation), clinical treatments (pharmacological treatment, TCM acupuncture, non-pharmacological combined treatment) and future research directions, which highlight the advantages of acupuncture and multi-method combined treatment. At present, some therapies in this field lack verification through large-sample studies. In the future, more studies need to be conducted to clarify the mechanisms, verify the efficacy and optimize the schemes, so as to provide references for clinical practice and scientific research of PDD.

Keywords: Parkinson's disease with depression; pramipexole, SSRIs, tricyclic antidepressants; acupuncture.

1. Introduction

Among middle-aged and elderly individuals, Parkinson's disease (PD) ranks as a prevalent neurodegenerative disorder. Clinically, its motor manifestations consist of muscle rigidity, resting tremor, postural balance impairments, and bradykinesia, whereas its key pathological characteristics are centered on the formation of Lewy bodies and the progressive degeneration of dopaminergic neurons in the substantia nigra [1]. It is worth noting that an increasing amount of evidence suggests that non-motor symp-

toms are frequently seen in Parkinson's disease patients. The management of PDD is more complicated than that of ordinary depression. It must balance improving depressive symptoms with avoiding exacerbation of PD motor symptoms, and its response to conventional antidepressants is often poorer due to PD-related neurobiological changes.

PDD severely impairs patients' quality of life, prognosis, and social function, worsens PD motor symptoms, increases care burden, and raises suicide risk and economic costs. Current PDD treatments mainly rely on drug intervention and psychotherapy, but individual efficacy varies greatly, and long-term use of medications may cause adverse reactions. Thus, in-depth exploration of PDD's pathological mechanism and optimization of clinical diagnosis and treatment strategies are crucial for PD research. Based on recent studies, this article systematically reviews the pathological mechanisms of Parkinson's disease with depression, existing clinical treatment methods, and future research directions, aiming to provide references for clinical practice and scientific research.

2. The Mechanisms of PDD

2.1 Neurotransmission Abnormalities

The mechanisms of PDD involve neurotransmission abnormalities, structural and metabolic changes in limbic networks, and inflammation. PDD involves progressive monoaminergic dysfunction, such as dopaminergic, serotonergic, cholinergic and noradrenergic dysfunction. First, decreased [^{11}C] RTI-32 binding (a DAT/NERT ligand) in the left ventral striatum may contribute to the development of depression. Reduced DAT levels in the bilateral putamen and caudate nucleus correlate with the severity of depression in PD, and presynaptic dopaminergic dysfunction may alter transporter availability. Furthermore, a D3/D2 receptor imbalance (a lower [^{11}C] -(+)-PHNO to [^{11}C] raclopride ratio in the striatum) may exacerbate the severity of depression and physical impairment in PD. Serotonergic pathways are critical in regulating mood, and their impairment is strongly linked to PDD. Noradrenergic denervation can also contribute to PDD, which is caused by reduction in NERT. It can affect the locus coeruleus, thalamus, and right amygdala, which disrupt stress regulation and emotional stability [2]. In addition, cholinergic neurodegeneration could contribute to PD depression, by disrupting acetylcholine signaling, impairing mood-regulating circuits. It can interact with serotonin and norepinephrine systems and further affect mood regulation [3].

2.2 Chronic Neuroinflammation

PDD may have an association with chronic low-grade neuroinflammation. Proinflammatory cytokines (IL-6, IL-1, IFN-γ, TNF-α) can be generated by microglial activation caused by trauma; these cytokines alter synaptic plasticity and brain structure, which may play a role in promoting neurodegeneration. Furthermore, IFN-γ stimulates Indoleamine 2,3-dioxygenase (IDO), which leads to decreased synthesis of tryptophan and serotonin, the latter being associated with depression and neurodegeneration. Inflammation can be associated with depression in PD by the increase of proinflammatory cytokines, such as IL-6 and the decrease in anti-inflammatory cytokines (e.g., IL-10) and neurotrophins (e.g., BDNF)—changes that can exacerbate neuronal damage and depressive symptoms [3].

3. The Treatment Strategy of PDD

The treatment strategy for PDD should take into account both motor and non-motor symptoms, with the core goal of improving the quality of life of patients. At present, there are various clinical treatment methods, which cover drug therapy, physical intervention and psychological support, etc. Drug therapy remains the mainstream, among which dopamine receptor agonists, selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs) are widely used and have shown different efficacy and safety. The following will introduce the research progress of various treatment methods in the treatment of PDD.

3.1 Drug Therapy Strategies

3.1.1 Pramipexole

A non-ergot dopamine D2/D3 receptor agonist is Pramipexole. In addition to improving motor symptoms, it also exhibits a definite antidepressant effect. Its mechanism of action may be related to the activation of dopamine D3 receptors in the midbrain limbic pathway and the regulation of mood and reward circuits. Pramipexole can significantly improve the depression score of patients with Parkinson's disease (PD), and its efficacy is superior to that of some traditional antidepressants. A randomized, double-blind, placebo-controlled trial was carried out by Barone et al [4]. Their findings showed that after 8 weeks of treatment, the mean HAMD score reduction in the pramipexole group (with a gradual titration and a target dose of 1.5 mg/day) was 6.8 points, a figure that is notably higher than that of the placebo group (3.5 points, $p < 0.001$). Additionally, the response rate in the pramipexole group was 45.5%, which was nearly twice that of the placebo group (23.3%). Nevertheless, when applied in clin-

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ical practice, it is still necessary to be vigilant about the possible side effects it may cause, such as nausea, daytime somnolence, orthostatic hypotension, particularly impulse control disorder (ICDs). Treatment should start with a low dose (e.g., 0.125 mg, three times daily) and involve gradual titration. At the same time, closely follow up on the patient's behavioral changes.

3.1.2 SSRIs antidepressants

By increasing the concentration of 5-HT in the synaptic cleft and selectively inhibiting the presynaptic membrane's 5-hydroxytryptamine transporter (SERT), SSRIs produce anti-anxiety and antidepressant effects. They are first-line drugs for treating various depressive disorders. In the treatment of PDD, commonly used drugs include sertraline, paroxetine and fluoxetine.

Owing to its relatively few drug interactions and weak inhibitory effect on the cytochrome P450 enzyme system (particularly CYP2D6), sertraline is often considered the preferred SSRI for PDD. A randomized controlled trial (RCT) on sertraline in the treatment of PDD showed that sertraline is statistically significantly better than fluoxetine (relative risk [RR] = 0.85, 99% CI = 0.74 to 0.98; number needed to treat [NNT] = 12) and other SSRIs as a class (RR = 0.88, 99% CI = 0.78 to 0.99; NNT = 17) and highlighted a consistent even though not statistically significant trend in favor of sertraline over many other antidepressants both in terms of efficacy and acceptability in a homogeneous and clinically relevant time frame of 8 weeks. Moreover, its effect in improving anxiety and depression symptoms has been widely recognized in clinical practice, with good tolerance and minimal impact on motor symptoms [5].

Paroxetine is one of the most effective anti-anxiety drugs among all SSRIs. Depression in patients with PDD often coexists with anxiety, panic attacks, and internal tension, and distinguishing between these symptoms can be challenging. Paroxetine can simultaneously target the two core symptoms of depression and anxiety, and is highly practical in clinical practice. In addition, paroxetine has a certain sedative effect. For PDD patients with severe insomnia, taking it in the evening can significantly improve sleep quality, but this advantage may weaken over time. However, the drug interactions and anticholinergic side effects of paroxetine are its biggest drawbacks. When using it, the pros and cons need to be weighed, especially for elderly patients, who should use it with caution.

Owing to the long half-life of normefluoxetine, its active metabolite, fluoxetine carries a comparatively low risk of withdrawal reactions when its use is discontinued. In addition, this drug has a certain activating effect and is suitable for patients with Parkinson's disease depression (PDD) presenting with symptoms such as fatigue and drowsiness. However, fluoxetine is a potent inhibitor of CYP2D6 and CYP3A4 in the cytochrome P450 enzyme system, and many Parkinson's disease treatment drugs (such as some dopamine receptor agonists and tricyclic antidepressants) are metabolized by these two isoenzymes. When used in combination, fluoxetine can inhibit the metabolism of these drugs, which leaded to an increase in their blood drug concentration and delayed clearance, thereby increasing the risk of adverse reactions or toxicity. Therefore, when using fluoxetine in combination with other drugs for treatment, special attention should be paid to the potential interactions between drugs. The clinical responses of patients and possible adverse drug reactions should be closely monitored. If necessary, the dosage should be adjusted in a timely manner to ensure the safety of medication [6].

3.1.3 Tricyclic antidepressants

By reducing levels of proinflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) and inhibiting NF-κB activation, TCAs including amitriptyline and imipramine bring about changes to inflammatory signaling cascades. Enhancing endothelial function and lowering oxidative stress are achieved by blocking the NLRP3 inflammasome and inhibiting pathways such as JAK/STAT, MAPK, and PI3K. Tricyclic antidepressants include nortriptyline, desipramine, and amitriptyline, which are considered as a potential treatment for depressive symptoms as they directly target the neurotransmitter deficits underlying depressive symptoms in PD.

Nortriptyline is a TCA used for depression treatment. The ADepT-PD trial is a multicenter, double-blind, randomized controlled study. It enrolled 408 PD patients with specific depressive subtypes and a BDI-II score of ≥14. These patients were assigned in a 1:1:1 ratio to the escitalopram group, nortriptyline group, or placebo group, with a 12-month treatment duration. The 8-week BDI-II score was set as the primary endpoint, and assessments of motor function, cognition, and other parameters were conducted at multiple time points. The results showed that nortriptyline can inhibit α-synuclein aggregation and neurotoxicity, and its anticholinergic properties can also alleviate tremors and insomnia in PD patients. Conducted as a long-term study in real-world settings of the UK NHS, this trial provides more comprehensive data on how medications impact motor symptom progression and other outcomes compared with similar studies [7].

Desipramine is a TCA that inhibits the reuptake of norepinephrine and serotonin, thereby increasing the levels of these neurotransmitters in the brain. Desipramine can treat depression in Parkinson disease by exerting its therapeutic effects. It inhibits the reuptake of norepinephrine at presynaptic nerve terminals, a mechanism that ultimately

results in an elevated concentration of norepinephrine within the synaptic cleft. This leads to increased noradrenergic neurotransmission, which can reduce depressive symptoms [8]. In Parkinson's disease, patients often experience depression as a common non-motor symptom. One of the mechanisms is the dysfunction of neurotransmitter systems including deficiencies in norepinephrine and serotonin. Therefore, desipramine can increase the levels of these neurotransmitters in the brain by inhibiting their reuptake, and this mechanism may help improve depressive symptoms in patients with Parkinson's disease.

Amitriptyline is a tricyclic antidepressant that affects several neurotransmitter systems. Like other TCAs, it helps increase the amount of serotonin and norepinephrine available in the synaptic cleft by preventing these neurotransmitters from being reabsorbed, a process that supports mood regulation in patients with Parkinson's disease—particularly given their norepinephrine and serotonin deficits. Amitriptyline can also produce off-target activity at histaminergic, muscarinic, and various other receptors. This is essential to depression in Parkinson disease patients, because in Parkinson disease, the connection between these receptors is disrupted. Therefore, Amitriptyline's actions on these receptors could regulate mood. Importantly, clinical studies suggest that Amitriptyline could improve the symptoms of depression in Parkinson disease. For example, a randomized study found that low-dose amitriptyline was effective in reducing depression and improving quality of life in PD patients, similar to sertraline (an SSRI). The research conducted a randomized study of 31 PD patients with major depression (per DSM-IV criteria); low-dose amitriptyline (25 mg/day) significantly reduced Hamilton Depression Rating Scale (HDRS-17) scores from 19.7 ± 2.8 at baseline to 8.6 ± 3.98 at 3 months ($P < 0.01$). The responder rate (≥50% HDRS reduction) was 72.7% (8/11 completers), and the remission rate (HDRS-17 < 7) was 45.4% (5/11 completers), which further confirm amitriptyline's efficacy in treating depression in PD [9].

TCAs are now only advised as second-line therapy for depression in PD patients due to their side effects. TCAs interact with a variety of receptors, such as adrenergic, histamine, and cholinergic receptors. Both therapeutic benefits and adverse effects, like sedation and anticholinergic effects, may result from these interactions. TCAs inhibit muscarinic acetylcholine receptors, which results in their anticholinergic effects, which include dry mouth, constipation, urine retention, blurred vision, and cognitive decline. These adverse effects can exacerbate pre-existing conditions or trigger delirium and confusion, which make them particularly problematic for elderly individuals [7].

3.2 Therapeutic Approaches of Traditional Chinese Medicine (Acupuncture)

Acupuncture, as a core external treatment method in Traditional Chinese Medicine (TCM), has gained increasing attention in the intervention of PDD in recent years. From the perspective of TCM, the onset of PDD is associated with "internal stirring of liver wind", "malnutrition of the heart spirit", and "qi and blood deficiency"; depressive symptoms fall under the categories of "yu zheng" (depressive disorder) and "xian bing" (hysteria), which are linked to an imbalance of the heart, liver, kidney, and spleen.

"Mind-Regulating Acupuncture Therapy" is an acupuncture approach focused on regulating mental state and calming the mind, with the goal of alleviating depressive symptoms, and is commonly used in conditions associated with emotional disorders. When applied to PDD treatment, it mainly selects acupoints such as Sishencong (EX-HN1), Baihui (GV20), Shenting (GV24), Neiguan (PC6), Taichong (LR3) and Shenmen (HT7), and combines with acupoint selection based on syndrome differentiation to achieve the effects of regulating mind to relieve depression and soothing liver to regulate qi. Clinical comparative experiments have proven that acupuncture can regulate qi and blood, balance yin and yang, calm the mind by stimulating acupoints, thereby improving depressive and motor symptoms. Mind-Regulating Acupuncture Therapy, which commonly uses acupoints like Baihui and Shenting, when combined with Western medicine, can significantly improve HAMD and UPDRS scores, as well as patients' sleep quality, fatigue status and daily living ability ($P < 0.05$) [10].

Modern studies have shown that acupuncture exerts antidepressant effects by regulating neurotransmitters, reducing inflammation, upregulating BDNF and regulating brain function networks. Acupuncture (especially Mind-Regulating Acupuncture Therapy) shows promising prospects in PDD treatment. In the future, more large-sample trials are needed to verify its efficacy and explore its mechanisms, so as to provide scientific evidence for the application of TCM.

3.3 Combination Therapy with Non-drug Measures

The combination of conventional medications (including Western and Chinese medicines) and acupoint therapy which is a non-pharmacological intervention encompassing acupuncture, moxibustion and acupressure, demonstrates superior efficacy in treating Parkinson's disease-related depression compared with pharmacotherapy alone. Data from 28 randomized controlled trials showed that the combined therapy had a 25% higher effective

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rate than conventional medication or non-drug treatment alone (risk ratio 1.25). A subgroup analysis was conducted on 20 randomized controlled trials, which compared the combination of acupoint therapy and Western drugs against Western drugs used alone. The analysis confirmed that the effective rate of the combined approach was 20% higher with a risk ratio of 1.2. Subgroup analysis of 10 randomized controlled trials (acupoint therapy + drugs vs. drugs alone) showed greater reductions (weighted mean difference = -2.1; $p < 0.00001$), and 3 randomized controlled trials (acupoint therapy + other therapies) also confirmed superiority (weighted mean difference = -2.26; $p < 0.00001$) [11].

Sun Hua et al. divided 60 patients into 3 groups (20 cases in each group), and administered rTMS, escitalopram, and the combination of the two for treatment respectively. Additionally, 20 healthy controls were set up, with a treatment course of 4 weeks. Results indicated that post-treatment, the combination group saw its HAMD score drop from 24.10 ± 4.19 to 10.75 ± 4.46, while its UPDRSII score fell to 9.60 ± 2.19—both of these outcomes were superior to those observed in the single-treatment groups. The BDNF mRNA levels of the three treatment groups increased, and that of the combination group increased from 0.56 ± 0.16 to 0.81 ± 0.08. This study attempted a combined intervention using multiple treatment methods and explored the role of BDNF. Compared with previous studies on single treatment, it is more comprehensive, which confirms that rTMS can be used for adjuvant treatment and that BDNF may be a potential target [12]. All the above studies indicated the therapeutic advantages of combined treatments using methods such as transcranial magnetic stimulation, traditional Chinese medicine, Western medicine and acupuncture.

4. Conclusion

Currently, the primary challenges in the field of Parkinson's disease with depression (PDD) include incomplete elucidation of pathological mechanisms. Conventional treatments require balancing the alleviation of depressive symptoms with the management of motor symptoms. Single-drug therapies show inconsistent efficacy and are prone to side effects when used for a long time, while some treatment methods lack sufficient verification. Existing achievements include the identification of key mechanisms such as abnormal neurotransmission and inflammation. In pharmacological treatment, dopamine receptor agonists and specific antidepressants can simultaneously improve both motor and emotional symptoms. Non-pharmacological approaches such as Traditional Chinese Medicine (TCM) acupuncture and repetitive Transcranial Magnetic Stimulation (rTMS) have shown therapeutic effects. Combined multi-therapy approaches (e.g., combination of medication with acupuncture or physical intervention) demonstrated better efficacy than single treatments. Potential therapeutic targets have also been identified. These achievements provide a basis for precise diagnosis and treatment, reduce the risk of drug side effects, and improve the effectiveness and safety of treatments. In the future, it is necessary to deepen research on pathological mechanisms, conduct large-sample trials to verify treatment methods, optimize combined treatment regimens, promote the integration of TCM and Western medicine, advance the development of target-specific drugs, and improve the diagnosis and treatment system for PDD.

Authors' Contribution

All the authors contributed equally and their names are listed in alphabetical order.

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