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Research Progress on Parkinson's Depression

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Abstract. Parkinson's disease has a high prevalence of depression, which is frequently undiagnosed and untreated and has a tight relationship to health-related quality of life. In order to study the latest findings in this field, This article summarizes the research related to PD depression from 2010 to 2022, respectively, from the pathogenesis research, including the influence of genes, nutritional factors, and proteins, and it also summarizes the current treatment methods for PD depression, including drug therapy, behavioral therapy, and psychotherapy. It also summarizes recent clinical trials, including new drugs and cognitive therapies. Finally, the future development direction of Parkinson's depression has been prospected. This paper finds that new genes and nutritional factors have been found in the pathological study of Parkinson's depression, and new combinations of drug therapy have been added to the treatment of Parkinson's depression, as well as new methods of using behavioral therapy and psychological intervention to assist the treatment.

Keywords: Parkinson’s depression, LRRK G2019S mutations, treatment, clinical report

1. Introduction

Parkinson's disease (PD) is a long-lasting neurodegenerative condition that manifests both motor and non-motor symptoms. Depression is a common comorbidity of Parkinson's disease (PD), with prevalence estimates ranging from 22% to 91% [1][2][3]. In older adults, estimates of concurrent anti-parkinsonian and antidepressant use range from 25% to 58% of patients [4], with selective serotonin reuptake inhibitors emerging as the most popular antidepressant. Additionally, depression has a significant role in predicting health-related quality of life, with increasing severity being correlated with a decline in quality of life.

Despite the negative effects on patients' lives, depression in PD patients is frequently underdiagnosed [5], possibly as a result of overlapping somatic symptoms and a lack of regular screening. This may lead to undertreatment of the disorder.

2. Currently predicted pathogenesis of Parkinson's depression

Intraneuronal dopaminergic neuron degeneration The characteristic neuropathological lesions of PD are lewy bodies located in the substantia nigra pars compacta. The loss of distinct noradrenergic and serotonergic neurons in PD is also well documented to occur, indicating that the neurological illness affects areas of the brain outside the midbrain. These neural networks work together to control mood and reward systems, as well as mood abnormalities in both PD patients and the general public [6].

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2.1. Gene

LRRK G2019S mutations were linked to increased depression ratings in two studies [7][8]. In a second study, relatives of probands with compound heterozygous PARK2 mutations who were unaffected were more likely to rate their depression symptoms higher than relatives of probands who did not have PARK2 mutations. There is still research that reveals a connection between serotonin transporter gene polymorphisms and depressed symptoms in Parkinson's disease [9]. In light of the lack of genotype or haplotype associations for the serotonin or dopamine transporter genes, it may be concluded that these common genetic variables have a little role in the emergence of depression in PD.

2.2. Neurotrophin

Neurotrophins like brain-derived neurotrophic factor (BDNF) control and encourage the living, adaptation, and development of central and peripheral neurons [10].

Additionally, studies conducted in vivo and in vitro have revealed that BDNF is essential for neurogenesis and osteogenesis in human bone [11].

2.3. Expression of alleles

The Val66Met (G196A, rs6265) polymorphism is a single nucleotide polymorphism (SNP) that resides in the BDNF gene's prodomain region. [12].

According to reports, people with PD who have the Met allele homozygosity (Met/Met) are more prone to exhibit apathetic sentiments than people without the Met/Met genotype.

2.4. Protein

Abnormal aggregation of syn disturbs basal and dynamic cortico BLA propagation, and these modifications may be connected to disturbed cortical control in the amygdala, which is a factor in the mental symptoms of PD [13]. The study came to the conclusion that synucleinopathies cause input-specific disruption of cortico-BLA synaptic connection and plasticity due to both increases in toxic characteristics and losses of normal function of Syn. The conclusions are consistent with clinical observations of reduced cortical regulation of amygdala activity, which may be a factor in PD patients' behavioral impairments.

2.5. Brain activity function

The cerebral modulation of amygdala activity is compromised in PD, according to compelling clinical data, which results in improper emotion valence encoding or deficiencies in connecting emotion to conduct.

3. Treatment

Given that Parkinson's depression is made up of two components—a mental disease and a behavioral problem—drug therapy and behavior therapy can be used to treat the condition, but it can be challenging to determine the best course of action. "Watchful waiting" and approaches to solve problems are reasonable first steps when life stressors are the patient's main concerns and it is unclear whether they have a mood disorder. A follow-up visit should be scheduled no later than two to three weeks later to evaluate the patient for a lingering mood disorder. Early intervention with occupational, physical, and speech treatments, home care services, and social workers increases patient and caregiver understanding of how PD affects them (education), makes positive illness better The impact of stresses that might become overwhelming and lead to depressive or anxious moods may be lessened via self-management (skill development) and assistance. It's also important to promote peer support programs, exercise, good psychological processes, sufficient sleep habits, and participation in physical activity.

The general population has shown that in order to achieve remission, aggressive phased care that is based on measurement methods, including several pharmaceutical trials lasting a number of months each, together with psychotherapy, may be necessary [14]. Depressive disorders in PD can be successfully treated with medication, somatic therapies, psychotherapies, rehabilitative therapies, or a

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combination of these therapies when they are actively and diligently pursued [15]. Even when an antidepressant prescription or other intervention has had a major impact, residual depression symptoms are frequently present. This suggests that ongoing monitoring and therapy modifications are necessary until the depressive condition has entirely subsided. A recovery-oriented strategy places an emphasis on a person's advantages and resiliency, increased functioning, pursuing personally important objectives, and an attitude of optimism and hope, even sometimes it is not possible to fully eradicate all signs and indications of depression. In spite of this, people with PD depression encounter obstacles to using mental health services, including inadequate health education, care access, the lack of doctors with PD understanding, and a preference for psychotherapy over medicine [16]. One approach that helps remove some of these obstacles and enhance results is multidisciplinary PD specialist team treatment [17].

3.1. Behavioral treatments

Despite having a successful track record with other elderly and neurological groups, psychosocial therapies like CBT have gotten less scientific attention in individuals with PD. For mild-to-moderate depressive disorders in PD, CBT can be utilized as a primary or additional kind of therapy in addition to drug changes. The intensity of the patients' symptoms decreased by 56% in an RCT of CBT for PD depression that lasted for 10 sessions and including some individuals who were already on antidepressants, compared to 8% for the control group [15]. In comparison to standard clinical management, participants in the CBT procedure, which included psychological activation, cognitive reorganization, anxiety reduction strategies, sleeping habits techniques, and caregiver assistance, experienced significant reductions in PD depression over the course of the 14-week intervention [18]. The CBT group also had a much higher rate of treatment responders (i.e., the number needed to treat was 2.1; the whole reduction in risk was 48%), and strong impact sizes were seen across the board for all depressed outcome measures. Similar outcomes were obtained with a case series design unique to CBT for PD depression, several uncontrolled pilot studies, and a telephone-based CBT course with ten sessions. Over the course of six months, a small (N=16) randomly selected studies of 12-session group psychotherapy that included a dramaturgical therapy session (i.e., role-playing everyday scenarios and addressing their implications in terms of psychology and society) was linked to considerable cuts in PD depression [19].

3.2. Medication principle

Depressive disorders in PD can be successfully managed with medication, somatic therapies, psychotherapies, recovery-oriented treatments, or an amalgamation of these therapies when they are addressed consciously and diligently. Since persistent monitoring and therapy modifications are necessary until the depressive illness entirely resolves, even when there has been a considerable response to an antidepressant drug or other intervention, are commonly present [20].

The data from drug trials of new medications is also more inclined to fulfill the standards for the classification "likely effective" than "efficacious", the highest level, because the majority of antidepressant drugs were created among the general public rather than in PD samples.

Nortriptyline, venlafaxine extended release, desipramine, citalopram, and paroxetine have all been shown to be effective when compared to placebo, though the timing of the antidepressant response has varied. In general, traditional antidepressants have been investigated in PD and proven to be well-tolerated and safe. For instance, nortriptyline revealed short-term superiority over placebo (i.e., after 8 weeks), while both paroxetine and nortriptyline provided evidence of enduring maintenance of treatment improvements (i.e., after 6 months) [20]. Trials of antidepressants in all demographics normally exhibit a significant placebo effect, however, the early placebo effect is frequently not persistent, making it crucial to understand the consequences of maintenance medicine over time [21]. The goal of most treatment studies, which typically run 8–12 weeks, is to determine if one intervention is superior than a control. In contrast, sufferers are told to expect improvements in signs over time in clinical practice, with a complete reaction to antidepressants lasting up to 12 weeks, proceeded by the continuous enhancement of any lingering symptoms. When the patient has received the maximum recommended

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dosages and a response is not shown within 12 weeks, the intervention is deemed useless for that patient. Adjustments to the medicine are necessary when there is minimal clinical response at any point, even after the first 12-week test, and particularly if there are indications of relapse or recurring depressive symptoms.

With varying degrees of success, The use of dopamine agonists as the primary treatment for PD depression has been studied[22].

Over a 12-week period, pramipexole proved successful in lowering depression symptoms despite its small effect sizes [23]. Trials of pramipexole that were open-label and randomised also showed antidepressant effects. Despite mood measurements not being the main outcomes, the findings from prior blinded studies in PD are ambiguous or unfavorable for depression. Alternative therapies are being investigated in tiny RCTs with intriguing outcomes, in which left prefrontal cortex was repeatedly stimulated with transcranial magnetic stimulation and omega-3 fatty acids.

3.3. Mental health counseling

Antidepressant medicines are seldom chosen by depressed people over psychotherapy. Multidisciplinary PD expert team treatment is single paradigm that aids in overcoming some of these challenges and improving outcomes for patients with PD depression. It might be difficult for patients with PD depression to get mental health services.

For treatment delivery to overcome access limitations, the telephone has been studied. Providing CBT over the phone as opposed to in-person for primary care patients with depression resulted in decreased attrition and nearly similar reduction in depression at posttreatment, according to one trial [24]. It shows that as compared to face-to-face delivery, T-CBT increases adherence, but at the expense of a higher chance of inferior benefit maintenance after therapy ceases.

3.4. Other treatments

Electroconvulsive treatment (ECT) is recommended for people in the general population in situations of profound depression when a quick remedy is required, for instance, when a person exhibits psychosis, catatonia, or severe vegetative symptoms together with imminent hunger or suicidality.

Recovering from PD depression with repetitive transcranial magnetic stimulation (rTMS) is another viable alternative for therapy[25]. Level A evidence (definite efficacy) was attained for the following treatments: HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC) utilizing a figure-of-8 or an H1-coil for depression; Level B evidence (probable efficacy) was attained for the following treatments: HF-rTMS of bilateral M1 regions or the left DLPFC for improving motor impairment or depression, respectively, in Parkinson's disease [26].

4. Clinical trial report

4.1. Drug therapy: SAM-e: 2003-10-13~2016-7-13

Although PD and depression are frequently linked, traditional antidepressants are ineffective in PD patients and may even make their motor symptoms worse. SAM-e is marketed as a mood booster in the United States and is sold as a dietary supplement. SAM-e enhances dopamine transmission, may be advantageous to dopamine receptors, and may be an excellent substitute for the antidepressants now prescribed to people with PD. The aim of this study is to ascertain if SAM-e can effectively and safely treat PD-related depression. Escitalopram, a specific inhibitor of serotonin reuptake frequently prescribed for the depression therapy for PD, and placebo will be utilized to compare the effectiveness of SAM-e. The medication exhibited a general reduction in behavioral and mental symptoms in its patients.

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4.2. Device treatment

With the help of cognitive-behavioral therapy, patients with PD learn to be more conscious of their thoughts and feelings as well as to alter thought patterns and actions that might be connected to depressive symptoms.

5. Treatment of prospects

Successful treatment choices will not be achieved by a "one size fits all" approach in a precision medicine-based environment. When developing a treatment plan for a patient with a diverse condition, it is more likely to be beneficial to incorporate their unique traits, such as genetics, age, and sex. The greatest therapy outcomes for Parkinson's depression, which is characterized by both mental and behavioral abnormalities, can be reached by combining the two therapies.

6. Conclusion

This article reviews the research results of PD depression in the past ten years and summarizes several possible pathogenesis, treatment methods, and clinical trials. At present, the research on the mechanism of disease is still not accurate enough, and there are still no in-depth research results on the association between physiological changes and diseases, waiting for further exploration. In the future, we hope to have a mature treatment system for Parkinson's depression that can complement each other with psychiatric treatment and behavioral treatment to achieve better efficacy.

The data collected in this paper is comprehensive, but the analysis of the current development of data sources is insufficient. The finding clinical trials focus on the report of the review, but for the drug market development, the author can not find the relevant information and needs to conduct a broader search. In the future, more comprehensive studies are expected to be conducted in combination with the marketing situation of drugs. It is hoped that there will be a more comprehensive summary and analysis of the principles of the disease until the medical status quo and the development of the drug market. Research on Parkinson's depression still has a lot of potential to grow because the disease's basic mechanisms are still very much unknown. There will be more and more articles in this field. Constantly updating people's understanding of the disease is the most basic form of the development of medical technology.

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