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Review

Neurobiology of depression in Parkinson's disease: Insights into epidemiology, molecular mechanisms and treatment strategies

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ABSTRACT

Parkinson's disease (PD) is characterized mainly by motor dysfunctions due to the progressive loss of dopaminergic neurons. However, PD patients experience a multitude of debilitating non-motor symptoms, including depression, which may have deleteriously detrimental effects on life. Depression is multifactorial and exhibits a bimodal progression in PD, but its underlying molecular mechanisms are poorly understood. Studies demonstrating the pathophysiology of depression in PD and the specific treatment strategies for depression-like symptoms in PD patients are largely lacking, often underrated, under-recognized and, consequently, inadequately/under-treated. Nevertheless, reports suggest that the incidence of depression is approximately 20–30% of PD patients and may precede the onset of motor symptoms. Diagnosing depression in PD becomes difficult due to the clinical overlap in symptomatology between the two diseases, and the nigrostriatal dysfunction alone is insufficient to explain depressive symptoms in PD. Therefore, the current study provides an overview of the molecular mechanisms underlying the development of depression in PD and new insights into developing current antidepressant strategies to treat depression in PD. This review will identify and understand the molecular pathological mechanisms of depression in PD that will fundamentally help tailoring therapeutic interventions for depressive symptoms in PD.

1. Introduction

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders. It involves progressive loss of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) and loss of dopamine in the basal ganglia. The progressive dopaminergic neuronal death and the appearance of distinctive granular α-synuclein aggregates in spherical pale bodies as cytoplasmic inclusions known as the Lewy body (LBs) are the signature neuropathological characteristics of PD (Goiran et al., 2022). PD is typically known for its cardinal motor manifestations like bradykinesia, muscular rigidity, resting tremor and postural instability largely due to progressive dopaminergic nigrostriatal degeneration in the SNpc and subsequent dopamine depletion in the basal ganglia. Also, non-motor dysfunctions like sleep disturbances,

Abbreviations: 5-HT, Serotonin transporter 5-hydroxytryptamine; 5-HTT, Serotonin transporter; 5-HIAA, 5-hydroxy indole acetic acid; 5-HTTLPR, serotonin-transporter-linked promoter region; 6-OHDA, 6-hydroxydopamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AVP, Arginine vasopressin; BDI, Beck Depression Inventory; BDNF, Brain-derived neurotrophic factor; CESD, Center for Epidemiologic Studies Depression Scale; CNS, Central nervous system; CSF, Cerebrospinal fluid; CRH, Corticotropin-releasing hormone; DAT, Dopamine Transporter; DSMMD, Diagnostic and Statistical Manual of Mental Disorders; GABAergic, gamma-aminobutyric acid-ergic; GMS, Geriatric Mental State; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton Depression Rating Scale; HPA-axis, Hypothalamic Pituitary Adrenal-Axis; ICD-9 CM, International Classification of Diseases, ninth revision, Clinical Modification; IDO, Indoleamine-2, 3-dioxygenase; IRR, Incidence Rate Ratios; LC, Locus coeruleus; L-DOPA, L-3,4-Dihydroxyphenylalanine; LRRK2, Leucine-rich repeat kinase 2; LB, Lewy body; MADRS, Montgomery–Asberg Depression Rating; MAPK, Mitogen-activated protein kinase; MAO, Monoamine oxidase; NMSQ, Non-motor symptom quest; NE, Norepinephrine; NPI, Neuropsychiatric Inventory; PVN, Paraventricular nucleus; PD, Parkinson's Disease, PDQ, Parkinson Disease Questionnaire; QIDS-J, Quick Inventory of Depressive Symptomatology-Japanese, SDS, Self-rating Depression Scale; SSRIs, Selective serotonin reuptake inhibitors SNpc, Substantia Nigra pars compacta; STN, subthalamic nucleus; TCA, Tricyclic antidepressants; TRD, treatment-refractory depression; TI, Tremor Index; TNF, Tumor necrosis factor; UPDRS, Unified Parkinson's Disease Rating Scale.

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sensory abnormalities, autonomic dysfunctions and behavioral changes, including depression, are intrinsic and almost inevitably emerge with PD progression (Borgonovo et al., 2017). Depression, in particular, is the most common and frequent non-motor symptom that occurs across all stages of PD. The impact of depression on the quality of life is more significant and severe compared to the other motor and non-motor symptoms in PD patients. The onset of depressive-like symptoms sometimes precedes the motor symptoms, may represent the first manifestations of PD and even become severe during the later stages of PD progression leading to severe disability and impaired quality of life (Pereira et al., 2017). After the synucleinopathies of the basal ganglia, the LB pathology may spread to the mesolimbic dopamine system, which connects the ventral tegmental area (VTA) to the limbic regions of the nucleus accumbens (NAc), forming a neural circuit that regulates the emotional conditioning. This mesolimbic dopamine reward circuit is disrupted in the early stages of PD, heralding nigrostriatal denervation and other dopaminergic dysfunctions (Muñoz et al., 2020). The development of depressive-like symptoms in PD results predominantly from neurotransmitter dysregulations beyond the dopaminergic system that may include serotonergic, noradrenergic, and cholinergic nuclei in the brainstem. Although depression is a pretty disabling manifestation of PD and extra-striatal and nigral dopamine denervation have been implicated, the exact underlying neuropathological mechanisms in PD remain to be elucidated. Even though almost half of the PD patients exhibit depressive-like symptoms, only about 26% receive treatment (Galts et al., 2019). Despite its high clinical prevalence and impact on the quality of life, the prevalence of depression in PD is inadequately documented; therefore, community-based, controlled, large and well-designed prospective studies demonstrating efficacious and well-tolerated treatment strategies against depression in PD are warranted. The early diagnosis of depression in PD can help in the more prompt treatment and, if left unrecognized and untreated, can adversely affect the quality of life, which can have therapeutic and societal implications. Here, we provide a current perspective on the epidemiology and aetiology of depression in PD as well as the effective treatment intervention for depression in PD. This review also highlights how depressive conditions in PD often overlap and overcomplicate the diagnosis and management that arise as a result. In addition, studies investigating the incidence of depression in PD are outlined.

2. Epidemiology of depression in Parkinson's disease

Depression is one of the most debilitating forms of psychopathology and a major cause of disability worldwide. Depression is one of the most common comorbidities of neurodegenerative diseases like Huntington's disease, amyotrophic lateral sclerosis, and Alzheimer's disease; however, it is even more prevalent or severe in PD and predates the onset of motor symptoms, suggesting that the onset of depression-like symptoms is a manifestation of PD (Nagy and Schrag, 2019). Depression is highly prevalent and one of the most disabling aspects that adversely affect the severity and quality of life in PD. The prevalence of depression-like symptoms is higher in PD than in other chronic and disabling disorders. According to reports, patients with PD are more likely to acquire depression than normal healthy individuals (Gou et al., 2018). The confluence of somatic symptoms of depression with other PD symptoms complicates the incidence of depression in PD. There is a consensus that reports on the prevalence of depression in PD are not fully understood. Nevertheless, there is compelling evidence that depression occurs at some time during PD progression (Pereira et al., 2017). The methods for reporting the prevalence of depressive-like disorders in PD consider various diagnostic procedures and contexts. Previous studies report that the prevalence of depression-like symptoms in PD varies considerably due to inconsistent validation and sampling procedures. Depression is observed in approximately 20–30% of patients with PD; however, the prevalence rates vary from 3% to 80% and are often persistent. (Ryan et al., 2019). According to recent epidemiological research, the prevalence of major depression (i.e., more severe) is approximately 5− 20%, dysthymia is 13%, and non-major forms of depression (i.e., minor or subsyndromal depression) in 10− 30% of PD patients (Weintraub and Mamikonyan, 2019). In cross-sectional studies, the prevalence of depression-like symptoms is between 20% and 49% (Marsh, 2013). While depression is also common in the general population but the prevalence of depression in PD patients is lower in the general population (8.1%) compared to out-patient (24.0%) and inpatient (21.7%) hospital settings (Leentjens, 2011). The most frequent and clinically significant depression-like symptoms occur in between 40% and 50% of all PD cases; thus, almost half, up to 50% of patients with PD, experience depressive-like symptoms at some time during PD progression (Cong et al., 2022).

The incidence of major depressive-like disorders was 19% in research studies that used a semi-structured interview to determine a diagnostic and statistical manual of mental disorders (DSM) criteria and 7% in studies that adopted DSM criteria that did not use a structured interview (Schrag and Taddei, 2017). Older people overall have a greater risk of developing depressive disorders (about 11%) than the normal general population (about 7%) and therefore are at greater risk of developing depressive-like symptoms in PD (Hemmerle et al., 2012). Community-based studies tend to reflect lower prevalence figures, and there does not appear to be a gender difference. In addition, studies reported clinically relevant levels of depressive symptoms without a proper diagnosis in 35% of patients (Ryan et al., 2019). These variabilities are primarily due to different settings, sampling methods, case ascertainment, diagnostic approaches and statistical measures of the various studies. These studies on the prevalence of depression in PD patients suggest that depression may develop at any stage during the disease progression. The depressive-like symptoms usually appear 4–6 years before the onset of motor symptoms after PD diagnosis (Ishihara and Brayne, 2006). Following the diagnosis of PD, the annual prevalence of newly diagnosed depression-like symptoms in major depression range from 1.86% to 10%, which may have a long-term or recurring course (Marsh, 2013). In addition, 16% of de novo PD patients experience incidental depression that previously did not have any depressive disorders, and about 10–15% of PD patients develop depressive disorders after PD diagnosis (Jellinger, 2022). Over all one in five PD patients have depressive disorders that develop impaired cognitive and executive functions and poorer quality of life.

Depression is associated with worsened motor dysfunctions and the severity of disease progression in PD patients. Previous studies have suggested an average time of around six years between developing depression-like symptoms and the appearance of motor symptoms (Schapira et al., 2017). The likelihood of depression is higher in the years preceding the PD diagnosis, suggesting that the progression of PD results in prodromal mood disturbances before the motor dysfunction appears (Postuma et al., 2012). Other studies have reported a higher risk for most neuropsychiatric symptoms as the severity of PD increases, but this does not always correlate with the age and time of onset of PD. (Rai et al., 2015). However, studies show that patients who develop PD at a young age have a higher rate of developing depression-like symptoms than those who develop it later in life (Dallé and Mabandla, 2018). Also, reports suggest the relationship between depression and the increasing severity of PD symptoms is not linear; it is rather biphasic, and comorbidity between depression and PD is higher during the early and late phases of PD progression (Galts et al., 2019). Other studies report that PD patients exhibit depression-like disorders during all stages of PD (Hemmerle et al., 2012). The severity of motor dysfunctions increases, and PD's duration and pathophysiology are longer in PD patients exhibiting depressive-like disorders than in those not showing depression-like symptoms (Yadav and Kumar, 2022). These findings suggest that depression in PD is likely a consequence of PD progression, and there may be a convergence of the two diseases. Therefore, depressive-like disorders are not necessarily a preclinical manifestation of PD-associated neurodegeneration but may be an active component of

the PD-related neurodegeneration process.

3. Diagnosis of depression in Parkinson's disease

Depressive-like disorders develop in 40− 50% of PD patients, only around 26% get treatment, and 20–60% are unrecognized or untreated (Ryan et al., 2019). Because the two diseases clinically overlap, diagnosing depressive-like symptoms in PD can be particularly difficult (Galts et al., 2019). Depression in PD is diagnosed primarily by depressive disorders, including emptiness and hopelessness, being emotionally restrained and anhedonia. PD patients suffering from depression include depressive disorders like dysphoria, pessimism, and anxiety (Laux, 2022). Recognizing the symptoms and subsequent need for treatment can be overshadowed by the overlap of various symptoms common to both diseases. The overlap of somatic and neurovegetative symptoms like fatigue, psycho-agitation, impaired concentration, and insomnia makes it difficult to identify and diagnose accurate depression-like symptoms. This may, in turn, contribute to either under-diagnosis or under-treatment and over-diagnosis or over-treatment of depression in PD. Diagnosing depression in PD is also complicated by the overlap of somatic symptoms in PD and psychological symptoms of depression (Conroy et al., 2020). These psychological signs of depression correspond to the motor and non-motor manifestations of PD (Dallé and Mabandla, 2018). For instance, hypophonia, soft speech due to incoordination of vocal musculature and bradykinesia, and impairment of voluntary motor control both conditions resemble the psychomotor dysfunctions in depression. Also, the appearance of some non-depressed PD patients (i.e., bradykinesia) can sometimes be confused with PD patients with severe depression. Depression in PD is also difficult to diagnose since many symptoms of depression, such as lack of sleep, loss of appetite, psychomotor slowness, and poor attention, may be caused by PD pathogenesis (Galts et al., 2019). These symptoms in PD may overshadow the underlying depressive disorders, or alternatively, depression may be over-diagnosed and undertreated. Depressive disorders predate PD diagnosis in about 30% of patients and may appear years, if not decades, before the onset of motor symptoms. Therefore, determining whether the motor dysfunctions appeared before or after the onset of depressive-like symptoms will help diagnose depression and PD-associated symptoms.

To avoid under or over-diagnosis of depression in PD, inclusive diagnostic frameworks, including DSM criteria for major, moderate or subsyndromal depressive disorders and the International Statistical Classification of Diseases and Related Health Problems for diagnosing depression were adopted (criteria for mild or severe depression) (Gallagher and Schrag, 2012). DSM-IV-R major depression diagnosis in PD identifies at least one core symptom like depressive moods or anhedonia and at least 5 or more symptoms like drastic weight loss, lack of sleep, dysfunctions in the psychomotor, feeling of worthlessness or guilt, lack of decisiveness and recurrent thoughts of suicide (Han et al., 2018). While clinical symptomatology differs, the DSM-IV standards appear genuine and correct. Of 173 PD patients, around 30% met the clinical standard for major depressive disorders, 20% for dysthymic conditions, 10% for minor depression and 8% for subsyndromal depression (Starkstein et al., 2008). Other studies have reported a large number of patients fitting these standards, despite the DSM-IV measures detecting severe statistically significant depressive disorder (Starkstein et al., 2011). The clinical diagnosis of depressive disorders in PD is not primarily concerned with physical symptoms. Some reports suggest that specific somatic symptoms such as psychomotor slowdown, fatigue, and anxiety do not clearly distinguish between patients suffering from depression and those who do not (Fried, 2015). However, primary signs, such as low mood or lack of interest and non-somatic signs, such as a sense of futility and suicidal tendencies do (Kendler, 2016). Therefore, somatic symptoms are significant for diagnosing depression, especially in the end, but they might be less critical in differentiating depression and non-depression-like symptoms in PD. The underlying metabolic disturbances of serum B12 level, thyroid levels, comprehensive metabolic process and complete blood profile that results in depression-like symptoms should be screened and need special attention. Depression in the general population is assessed by different rating scales such as Zung Self-rating Depression Scale (SDS), Montgomery Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Centre for Epidemiologic Studies Depression Scale (CES-D) and Hamilton Rating Scale for Depression (HAM-D) (Bech, 2006). All these screening tests measure, screen and diagnose the severity of depression-like symptoms, including psychological and somatic symptoms of depression. However, they have also been utilized in PD to validate the depression assessment scales in PD (Lopez et al., 2018). Other studies have shown that these screening tools have good reliability and validity in measuring depressed symptoms in PD (Torbey et al., 2015). The overlapping PD and depression symptomology is given in Fig. 1.

4. Pathophysiology of depression in Parkinson's disease

The etiopathophysiology of depression in PD is unclear and remains largely unexplored. There is no consensus on whether the pathophysiology is organic, reactive, or a combination of both. Depression in PD is rather multifactorial, heterogeneous, and complicated that may arise due to the interaction of various psychological and neurobiological factors. Psychological factors and motor dysfunctions may be the most likely underlying mechanisms in developing depressive disorders in PD patients. However, it may result from the underlying disease process rather than solely a reaction to motor disabilities. Although reports suggest that depression in PD is a natural consequence of progressive neurodegeneration associated with PD, depression does not appear to be a straightforward reaction to the severity of the physical impairment in PD (Menon et al., 2015). Studies suggest that developing depressive-like symptoms in PD may not merely be a psychological response to PD diagnosis but may be secondary signs of the already PD-mediated neurodegeneration (Mueller et al., 2018). One opinion contends that depression may occur as an early manifestation during the prodromal phase before the onset of motor dysfunctions in PD. This may be supported by the fact that during the onset of depressive disorders in PD, there is an extensive loss of serotonergic raphe neurons in the median and dorsal raphe nucleus, a region implicated in depression much before the loss of dopaminergic neurons in SNpc (Galts et al., 2019). Another outlook suggests that premorbid depression may increase the risk of developing PD. Psychological conditions like depression (see Section 4.1) may increase the risk of developing pathophysiological symptoms in PD. PD-related neurodegeneration likely occurs several decades before the onset of motor symptoms. Also, similar to other diseases, the psychosis of PD diagnosis and the fear of its consequence may develop depression-like symptoms in PD (Schapira et al., 2017). Clinically various factors associated with depression have been implicated in the pathogenies of PD. These include the stage and duration of the disease, the severity of motor dysfunctions and treatment strategies (Bang et al., 2021). However, the occurrence of depression-like symptoms does not parallel the course and event of motor dysfunctions in PD patients. The development of depression predates the onset of motor symptoms in PD. Yet, some studies argue that depression develops in PD only after the disease is diagnosed (Hemmerle et al., 2012).

There appear to be three possible subtypes of comorbid depressive disorders in PD. (Even and Weintraub, 2012). The first subtype is nonspecific casual comorbidity between depression and PD, in which patients may experience depression-like symptoms even if they do not develop PD. The second subtype is a nonspecific reactive comorbid condition between depression and PD, in which patients are more prone to develop depression if they have other chronic debilitating diseases in addition to PD. The third and most relevant subtype is the specific comorbidity between depression and PD, in which patients have depression-like symptoms directly correlated with PD pathogenesis. Thus depression in PD may be a particular entity only in some PD

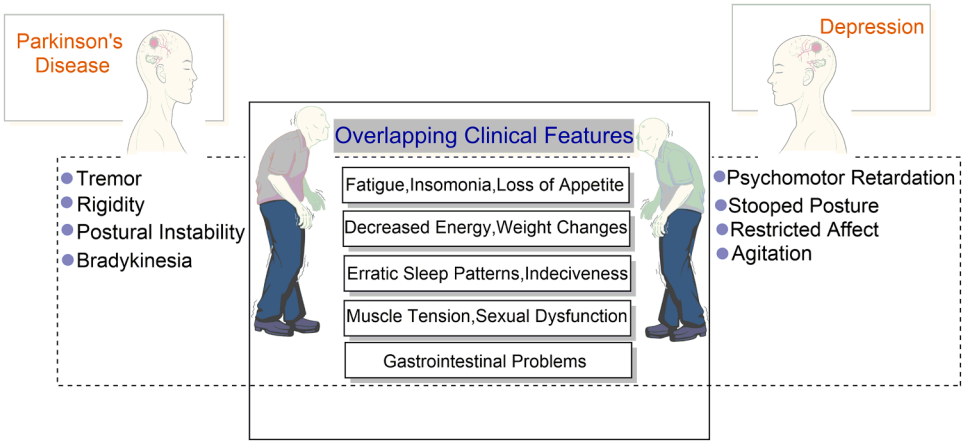

Fig. 1. Diagrammatic illustration of neurobiological mechanisms in the pathophysiology of Parkinson's Disease and depression. Decrease in neurotransmitters levels, a dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, neuroinflammation, abnormal hippocampal neurogenesis (CA1, CA3, DG), reduction of trophic support (BDNF, TrkB) together with genetic predispositions is the possible mechanisms that may contribute to the development of depression in PD. Abbreviations: CA, Cornu Ammonis; DG, Dentate gyrus; BDNF, Brain-derived neurotrophic factor; IL-1, Interleukin 1; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor-α; Trk-B, Tropomyosin receptor kinase-B.

patients but certainly not in all and is rather heterogeneous and multifactorial in most cases. Factors like the lag time between the diagnosis, under-recognition of depressive disorders and insidious onset of PD make it very difficult to determine the exact pathophysiology between depression and PD. Therefore, prospective studies focusing on the parallel etiologies of depression and PD are warranted. The studies investigating the development of depression in PD are summarized in Table 1.

4.1. Neurobiological basis of depression in Parkinson's disease

Various genetic vulnerabilities, cognitive predisposition, neurobiological and psychological factors are likely reasons for developing depressive-like disorders in PD (Weintraub and Mamikonyan, 2019). In particular, neurobiological factors have been associated with the third developing subtype of depression in PD patients. Neurobiological factors provide a basis for developing depression in patients with PD compared to PD patients without depression. Neurobiological factors associated with PD progression provide a backdrop for the high incidence of depression-like disorders in patients with PD compared to the chronic disabilities in non-PD patients (Toomsoo et al., 2017). Distinctive neuropathological brain changes characterize PD. These neurobiological changes lead to depression-like symptoms in PD and may vary dynamically in progression (Prange et al., 2022). Degeneration of dopaminergic nigrostriatal neurons with LBs is the primary neuropathological characteristic of motor dysfunctions in PD. Neurological changes do not only extend beyond the mid-brain but also involve a progressive degeneration of noradrenergic and serotoninergic neurons. Together they regulate mood and reward systems in the general population and PD patients in particular (Lian et al., 2019). The neurobiological changes during PD are specifically restricted to subcortical nuclei known as the basal ganglia, which regulate motor function, learning, executive functions and emotions. The basal ganglia mainly comprise the striatum, substantia nigra, and subthalamic nucleus and are extensively interconnected with the cerebral cortex, thalamus, and brainstem. Studies suggest that the basal ganglia regulate motor functions and are likely involved in cognitive and emotional processes (Sgambato-Faure and Tremblay, 2018). Extensive atrophy in basal ganglia circuitry projecting to the inferior frontal lobe play a vital role in the development of major depressive disorders in PD (Kendler, 2016). Structural brain abnormalities like volumetric reductions in prefrontal, parietal, and temporal regions; cortical thinning in the prefrontal, temporal, dorsal anterior cingulate cortex, and dentate gyrus correlate with depressive disorders in PD (Jellinger, 2022). Depression in PD is thus largely due to the neuropathological changes in neural networks like deterioration of cortical, subcortical nuclei, frontal lobes and basotemporal limbic circuits rather than a neurologic deficit of a discrete brain region. The neurobiological mechanisms in the pathophysiology of depression and PD are given in Fig. 2.

4.2. Neurotransmitter dysregulations during depression in Parkinson's disease

There are certain dysregulations in brain functioning, particularly in neurotransmitters and cytokines levels in PD. Dopaminergic pathways and neurotransmitters are adversely damaged during PD and likely have a crucial role in developing non-motor signs (Yadav and Kumar, 2022). Studies suggest that these dysregulations may be implicated in developing depression in PD (Dallé and Mabandla, 2018). The neurotransmitters like acetylcholine, particularly dopamine, serotonin and noradrenaline, are significantly decreased during the development of depression in PD or in general (Barone, 2010). Dysregulation of neurotransmitter levels could result from dopamine deficiency or changes in dopaminergic systems that could be implicated in developing depressive symptoms in PD (Healy-Stoffel, Levant, 2018).

4.2.1. Dopaminergic system

Progressive dopaminergic neuronal death in the nigrostriatal pathway plays an important role in developing depression and PD (Muñoz et al., 2020). A neural circuit between the VTA and orbitofrontal cortex may play a key role in developing depression in PD (He et al., 2021). Dopamine regulates motor and cognitive functions and significantly decreases in the basal ganglia through interaction with the thalamus and cerebral cortex, affecting motor function in PD (Borgonovo et al., 2017). The dopamine neurons of SNpc begin to degenerate, which in turn stimulates the ventral striatum involved in reward and emotions. These changes may partly account for the depressive-like symptoms that may predate motor dysfunction in PD (Leal et al., 2019). An interconnection between the ventral tegmental and orbitofrontal cortex may play a role in developing depression in PD. Dopaminergic neuronal loss in the ventral tegmental region and its cortical projections cause disturbances in limbic basotemporal areas, disrupting basal gland-thalamocortical circuits and dopamine levels. The decreased levels of dopamine in the thalamus during PD not only affect motor function but, because of the interconnection between the thalamus and the amygdala, such decreased dopamine levels also affects emotion (Ilkiw et al., 2019). Previous research has found lower dopamine levels in the caudate nucleus of the striatum in PD patients with depression compared to PD patients without depression. (Vriend et al., 2014b). Studies have reported low adherence to Striatal Dopamine Transporter (DAT) in patients suffering from depression compared to PD patients without depression (Vriend et al., 2014a). Dopamine deficiency generates dysregulations in the dopamine-mediated reward system, which can lead to disorders like anhedonia and, nearly always, alter reward function (Speranza et al., 2021).

Table 1
Studies investigating the incidence of depression in PD patients.

S. No	Study Design	Sample Size	Measurement Scale	Characteristics of depression in PD	Reference
1.	Prospective open-labelled	10 depressed parkinsonian patients	H.R.S.	Moderate to severe depressive-like symptoms	(Jouvent et al., 1983)
2.	Non-blind	30 patients with idiopathic PD	BDI	Mild depressive symptoms	(Mentenopoulos et al., 1989)
3.	Outpatient clinic	A consecutive series of 105 outpatients with PD	DSM-III	Minor and major depression	(Starkstein et al., 1990)
4.	A multicenter study	13 patients with idiopathic PD	HARD	Mild to moderate depression	(Rondot and Ziegler, 1992)
5.	Retrospective study	339 patients with PD	DSMMD	Higher incidence of depressive disorders	(Dooneief et al., 1992)
6.	A prospective longitudinal study	A consecutive series of 105 patients with PD	DSM-IV	Major depression	(Starkstein et al., 1992)
7.	Population-based study	73 subjects with PD	DSM-III	Major depressive disorder	(Hantz et al., 1994)
8.	A Community-Based Study	245 PD patients	DSMMD-III	Major depressive disorders	(Tandberg et al., 1996)
9.	Outpatient clinic	109 patients with PD	DSM-III-R	Major depression	(Liu et al., 1997)
10.	A Community-Based Study	245 PD patients	DSMMD-III	Major depressive disorders	(Tandberg et al., 1998)
11.	Outpatient clinic	63 non-demented PD patients	HAMD-17, MADRS and DSM-IV	Major depression	(Leentjens et al., 2000)
12.	Prospective open-label	A subgroup of 111 PD patients	UPDRS CESD, PDQ-39	Mild depression	(Happe and Berger, 2001)
13.	Prospective randomized study	41 non-demented PD patients	MADRS	Mild or moderate depression	(Rektorová et al., 2003)
14.	Randomized, double-blind	30 PD patients	TI and UPDRS	Moderate depressive disorders	(Navan et al., 2003)
15.	A controlled, non-randomized study	30 consecutive PD patients	BDI	Mild to severe depression	(Di Rosa et al., 2003)
16.	A follow-up of two years, non-randomized study	30 consecutive PD patients	BDI	Mild to severe depression	(Morgante et al., 2004)
17.	Population-based study	162 individuals diagnosed with clinically probable PD	GDS	Some signs of depression	(Kang et al., 2005)
18.	Prospective non-randomized study	25 PD patients	HAMD	Mild depression	(De Gaspari et al., 2006)
19.	Open-label, non-blind randomized controlled trials	67 Parkinsonian outpatients	DSM-IV HAMD	Major Depression	(Barone et al., 2006)
20.	A randomized, controlled study	393 subjects with PD	BDI-II	Moderate depression	(Pahwa et al., 2007)
21.	NMS Quest	545 PD patients	NMSQ	Prevalence of Non-motor Symptoms	(Martinez-Martin et al., 2007)
22.	A double-blind, randomized, placebo-controlled study	48 non-demented PD patients	MADRS	Major depression	(Devos et al., 2008)
23.	A cross-sectional study	1351 consecutive non-dementia PD patients	HADS, NPI	Major depression	(Kulisevsky et al., 2008)
24.	A case study	14 PD patients	DSM-IV	Depressive or anxiety symptom	(Veazey et al., 2009)
25.	2 Clinical trails	413 clinical trial patients,	GDS-15	Significant depressive symptoms	(Ravina et al., 2009)
26.	Cluster analysis	175 patients with incident PD	NPI	Significant neuropsychiatric symptoms, including depression	(Aarsland et al., 2009)
27.	Cross-sectional study	422 clinic non-dementia PD patients	HAMD	Severe depression	(Nègre-Pagès et al., 2010)
28.	GEPAD Study	1449 outpatients with PD	MADRS	Moderate depression	(Riedel et al., 2010)
29.	PARKIDEP survey	1086 patients with idiopathic PD	MADRS	Major depression	(Vanderheyden et al., 2010)
30.	A randomized controlled trial	21 depressed patients with PD	DSM-IV	Depressive disorders	(Dobkin et al., 2011)
31.	A longitudinal study (PROMS-PD)	513 patients with PD	GMS, HADS	Depression and anxiety-related subtypes	(Brown et al., 2011)
32.	A population-based follow-up study between 1994 and 2005	3637 patients with PD	IRR	Risk of incident depression	(Becker et al., 2011)
33.	A randomized, double-blind, placebo-controlled trial	115 subjects with PD	DSM-IV, HAMD	Subsyndromal depression	(Richard et al., 2012)
34.	A nationwide population-based study	23,180 participants (4634 patients with depression and 18,544 controls)	ICD-9-CM	Moderate depression	(Shen et al., 2013)
35.	Cross-sectional study	142 PD patients	HADS	Moderate to severe depression	(Dubayova et al., 2013)
36.	Meta-analysis	Five clinic-controlled trials	HAMD	Depressive disorders	(Qiu et al., 2014)
37.	A Nationwide Cohort Study	1698 patients with PD	DSM-IV	Elevated risk of depression	(Hsu et al., 2015)
38.	A nationwide cohort study	140,688 cases of depression	ICD-9 code 311, ICD-10 code F32 or F33	Depressive symptoms	(Gustafsson et al., 2015)
39.	A systematic review and meta-analysis	21 studies	BDI, MADRS	Major depression	(Goodarzi et al., 2016)
40.	A systematic review	11 studies, including 342 patients	BDI	Mild to Major depression	(Wu et al., 2017)
41.	Inpatients and outpatients	2015 to December 2017	HAMD	Moderate depression	(Liu et al., 2018)
42.	A meta-analysis	5 cohort studies and 6 case-control studies	ICD, ICHPPC, DSM	Association between depression and subsequent risk of PD	(Wang et al., 2018)

(*continued on next page*)

Table 1 (*continued*)

S. No	Study Design	Sample Size	Measurement Scale	Characteristics of depression in PD	Reference
43.	A case-control study	353 newly-diagnosed PD patients	ICD-9-CM	Onset of depression	(Wu et al., 2018)
44.	A Multicenter Randomized Study	55 patients	QIDS-J	Depressive symptoms	(Takahashi et al., 2019)
45.	A randomized controlled trial	478 PD patients	HAMD	Mild to severe depression	(Lian et al., 2019)
46.	A randomized controlled trial	72 PD patients	HAMD	Depressive symptoms	(Dobkin et al., 2020)
47.	A nationwide nested case-control study	1767 PD patients	ICD-9-CM	Depression, anxiety disorders and sleep disturbances,	(Chang et al., 2020)
48.	A retrospective analysis of medical records	300 PD patients	HAMD	Anxiety and depression	(Su et al., 2021)
49.	A novel case-control investigation	124 subjects	BDI	Depression symptoms	(Jiménez-Cebrián et al., 2021)
50.	A systematic review and meta-analysis	14 randomized controlled trials involving 516 patients with PD	BDI, HAMD, CESD, POMS, SCL-90, HADS, CGI, QIDS-SR, MADRS, SDS.	Approximately 50% of PD patients suffer from depression	(Tian et al., 2022)

Glossary: BDI, Beck Depression Inventory; CESD, Center for Epidemiologic Studies Depression Scale; CGI, Clinical Global Impression; DSMMD, Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; GMS, Geriatric Mental State; HADS, Hospital Anxiety and Depression Scale; HAMD, Hamilton Depression Rating Scale; ICD-9 CM, International Classification of Diseases, ninth revision, Clinical Modification; ICHPPC, International Classification of Health Problems in Primary Care; IRR, Incidence Rate Ratios; MADRS, Montgomery–Asberg Depression Rating; NMSQ, non-motor symptom quest; NPI, Neuropsychiatric Inventory; PDQ, Parkinson Disease Questionnaire; POMS, Profile of Mood States; QIDS-J, Quick Inventory of Depressive Symptomatology-Japanese; QIDS-SR, Quick Inventory of Depressive Symptomology-Self-Report; SCL-90, Symptom Checklist-90; SDS, Self-Rating Depression Scale; TI, Tremor Index TI; UPDRS, Unified Parkinson's Disease Rating Scale.

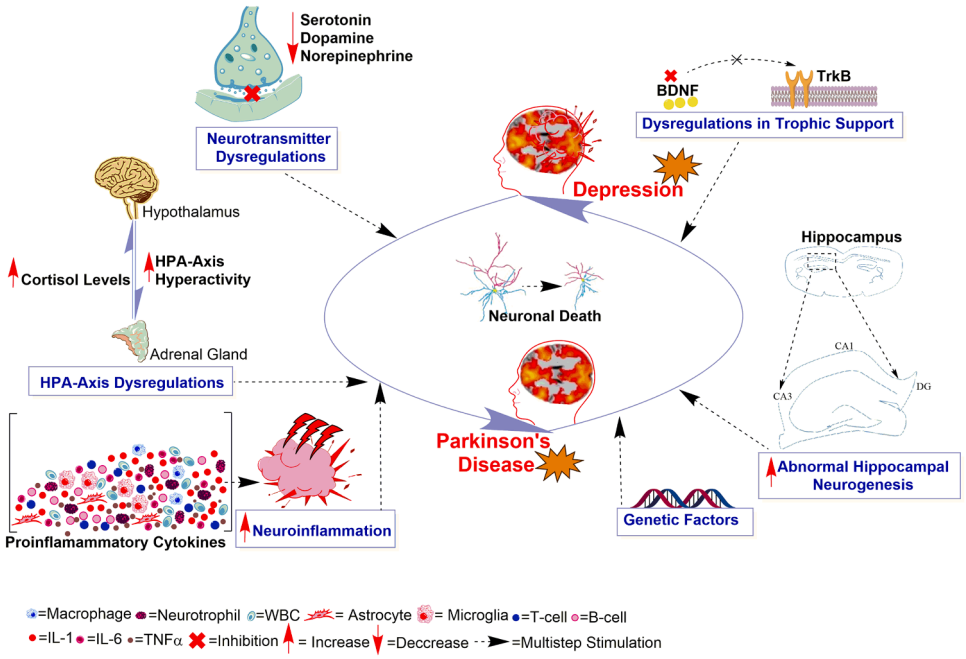

Fig. 2. Overlapping Parkinson's Disease and depression symptomology. The common clinical features of Parkinson's Disease and depression include low mood/sadness, anhedonia, fatigue, psychomotor dysfunctions, decreased concentration, insomnia, loss of appetite, worthlessness, and anxiety.

4.2.2. Serotoninergic system

The brainstem dorsal raphe nuclei, including the median raphe nuclei, constitute one-third of all serotonergic neurons in the brain and perform neuromodulation in the central nervous system (CNS). Activation of the dopamine type-2 receptor has excitatory effects on the serotonergic neurons by depolarizing them and facilitating the release of serotonin or 5-hydroxytryptamine (5-HT) in the dorsal raphe nuclei (Wang et al., 2019a; b). Studies have demonstrated the decreased striatal and extra-striatal levels of 5-HT, indicating the implications of serotonergic dysfunction in PD pathology-inducing depression (Maillet et al., 2016). 5-HT is secreted in the dorsal raphe nucleus and is transported from the synaptic cleft into serotonergic neurons, where it modulates various functions like mood and emotion (Dallé and Mabandla, 2018). Studies suggest that serotonergic neurons play an important role in cognition, emotion and motor function. Therefore, any imbalance in the serotonergic system may be a risk factor for the pathophysiology of motor and non-motor symptoms, including depressive symptoms (Maillet et al., 2016). The influence of 5-HT on dopamine neurons is conditional in sub-cortical regions and shows different physiological functions depending on its binding to a variety of distinct receptors, at least 14 other 5-HT receptors (De Deurwaerdère and Di Giovanni, 2017). 5-HT has been reported to induce the pre and post-synaptic excitation of Globus pallidus neurons via these different receptors. 5-HT modulates the functions of Globus pallidus, which in turn modulates basal ganglia circuity and controls limbic, cognitive, and motor functions. Decreased 5-HT levels may cause an imbalance in the basal ganglia activity resulting in the pathogenesis of PD, and its imbalance may also be neural mechanisms underlying depression in PD. 5-HT and its receptors have been reported to regulate the central dopaminergic activity in CNS by having excitatory or inhibitory effects

via its various receptors (Peters, Cheer et al., 2021). For instance, it is phasic and facilitates dopamine release via the 5-HT1A, 5-HT1B, 5-HT2A, 5-HT3, 5-HT4, and 5-HT7 receptors, inhibits cholinergic interneurons via 5-HT2C, 5-HT6 receptors (De Deurwaerdère and Di Giovanni, 2017). Activation of 5-HT2C receptors, in particular, inhibits the constitutive activity and release of dopamine by having phasic, evoked and tonic inhibitory effects on the basal electric activity of cholinergic dopamine interneurons (Lagière et al., 2020). Activation of 5-HT causes the fast release of dopamine in the nucleus accumbens mediated by 5-HT receptors and α-amino-3--hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). Their activation may also inhibit the activity of striatal projecting neurons by activating postsynaptic gamma-aminobutyric acid-ergic (GABAergic) inhibitory circuity (Spoida et al., 2014). This imbalance between serotonergic and dopaminergic neurotransmission may therefore be an underlying mechanism for the pathophysiology of PD (Pagano and Politis, 2018). Studies also suggest that an imbalance in the metabolisms of 5-HT receptors may be the underlying mechanism for developing depressive symptoms in PD (Wang et al., 2022). A recent study reported that dysfunction of monoaminergic 5-HT can also develop depressive symptoms in PD (Peters et al., 2021). Another study also showed that changes in 5-HT neurotransmission are involved in the aetiology of depressive disorders of PD (Liu et al., 2019). 5-HT reuptake sites are abnormally diminished in PD patients with or without depression. However, compared to non-depressed PD patients, the serotonergic neurons in the raphe nucleus degrade more severely in PD patients with depression (Martens and Lewis, 2017). The serotonergic neurons innervate the striatum, the amygdala, and the prefrontal cortex, which, together with the dorsal raphe nucleus, degenerate during the depression (Ryan et al., 2019). Low 5-HT levels and 5-hydroxy indole acetic acid (5-HIAA), a 5-HT metabolite, have been observed in PD patients with depression (Nagy and Schrag, 2019). Though studies have found reduced levels of 5-HIAA in PD patients with no depressive-like symptoms, the levels are substantially lower in PD patients with depression (Bang et al., 2021). Lower levels of 5-HIAA and cerebrospinal fluid (CSF) in PD patients correspond to depressive symptoms such as psychomotor dysfunction and loss of self-esteem (Kaiserova et al., 2021). Serotonin transporter (SERT) or (5-HTT) and functional polymorphism of 5-HTT have pathologically lower CSF levels in PD patients with depression (Weintraub and Mamikonyan, 2019). These findings hint at the possibility of a role of serotoninergic pathology in PD patients.

4.2.3. Noradrenergic system

Recent studies suggest that α-synuclein aggregates do not appear in different parts of the brain simultaneously; they instead appear in the gut and travel to the brain via the vagal nerve, where they spread sequentially through 6 different stages as defined by Braak et al. (Zhou et al., 2019b). The aggregation of α-synuclein appear first in locus coeruleus (LC) and may be with more severe magnitude among all the interconnected nuclei and is therefore regarded as the principal noradrenergic nucleus in the CNS (Zhou et al., 2019b). LC innervates and influences the activity of nuclei all over the brain, including the VTA and SNpc. Although LC does not innervate the nuclei that are innervated by the dopaminergic system, it modulates the neurotransmission of dopamine distally (Paredes-Rodriguez et al., 2020). The accumulation of α-synuclein in LC results in LC neuronal loss and degeneration, which may result in the reduced innervations of LC target nuclei and decreased levels of NE in several areas of the brain (Paredes-Rodriguez et al., 2020). Motor functions in PD are attributed to the loss of dopamine levels, but dysregulations in the noradrenergic system have also been reported to mediate alterations in dopamine levels in the striatum and indirectly mediate motor functions in PD (Gaval-Cruz et al., 2016). The accumulation of α-synuclein causes morphological changes like constricted dendrites, swelling of cell bodies and mitochondria in LC. This results in the degeneration of noradrenergic axons, terminals, and NE in LC projection regions and causes noradrenergic dysfunction (Weinshenker, 2018). The LC mediates the activation of neuromodulators like BDNF, Galanin, neuropeptide Y, encephalin, and ATP. Therefore, noradrenergic dysfunction may result in neuroinflammation, alterations in trophic factors and oxidative stress in SNpc, thereby aggravating dopaminergic neurodegeneration in PD. Accordingly, the dysfunctional noradrenergic neurons may also play an important role in the pathogenesis of depression in PD. LC is the primary source of NE and is reported to get degenerated, thereby decreasing the levels of NE during the depression in PD (Dyer-Reaves et al., 2019). The locus coeruleus is particularly susceptible to pathology alterations, and its degeneration may occur during the depression in PD (Doppler et al., 2021). PD patients with depression exhibit spatial patterns of structural disintegration with extensive rostral and caudal cell loss in the locus coeruleus compared to PD patients with no depression (Madelung et al., 2021). The decrease in NE activity has been linked to decreased activity of NE neurons in the locus coeruleus, which is more pronounced in PD patients with depression than in PD patients without depression (Doppler et al., 2021). The degeneration of the locus coeruleus might follow a disease-specific rostrocaudal pattern which is more severe in PD patients with depression and seems to have been spared in non-depressed PD patients (Oertel et al., 2019). The degeneration of the locus coeruleus hypersensitizes the noradrenergic receptors to trigger the switch between "on" and "off" and indirectly regulate the mood and sleep disorders in PD (Weinshenker, 2018). These reports suggest that NE deficiency can lead to depression in PD.

4.3. Dysregulations in HPA-axis

The hypophyseal portal system connects to the anterior part of pituitary glands and forms the Hypothalamic-Pituitary-Adrenal Axis (HPA-axis), which upon secretion in response to any aversive stimuli releases corticotropin-releasing hormone (CRH). Previous studies suggest that perturbation or hyperactivity of the HPA axis is a common characteristic of major depressive disorders (Ahmad et al., 2021). Reports also suggest that dysregulation and decreased feedback inhibition of the HPA-axis have been linked to the pathogenesis of PD (Aarsland et al., 2012). However, studies on the exact role of the HPA-axis in PD patients suffering from depressive disorders are scarce. Nevertheless, studies suggest a psycho-neuroendocrinological link between chronic stress in depression and PD (Hou et al., 2014). A review reported that stress response and the HPA axis are dysregulated in PD patients with depressive disorders (McEwen, 2008). Although the direct effect of dysregulated HPA-axis function in PD is not adequately determined, the role of cortisol in the long-term impact of chronic stress in PD is well documented. Chronic stress mediated by increased cortisol levels has been related to the onset and progression of depressive disorders (Warren et al., 2014). Similarly, higher cortisol levels in the blood reflect depressive symptoms in PD patients (van Wamelen et al., 2020). The increased cortisol levels in depression and PD patients suggest a potential common pathway between the two diseases. The elevated cortisol levels in PD patients have been largely related to depression-like symptoms (Bang et al., 2021). Dysregulations in the HPA-axis, mediated by high cortisol levels, were associated with depression scores in PD patients (Seifried et al., 2013). Similar observations were observed in another study that found lower 5-HT levels reduced the hypothalamic function via the corticotropin axis and subsequent cortisol release during the depression in PD patients (Müller and Muhlack, 2007). The incidence of dysregulations in HPA-axis functioning ranges between 35% and 65% in PD with depression (Soares et al., 2019). The HPA-axis dysregulations are coupled with increased cortisol levels, CRH and arginine vasopressin (AVP) neuro-peptide variance in the paraventricular nucleus (PVN) of the hypothalamus in depression patients (Sousa et al., 2014). Though, depressive symptoms in PD patients did not correlate with increased CRH-expressing neurons in the hypothalamic PVN (van Wamelen et al., 2020). However, a preclinical study found that chronic stress-induced depression exacerbated PD's behavioral

dysfunction and degeneration of the dopaminergic nigrostriatal system (Hemmerle et al., 2014). Chronic stress-induced HPA dysregulation may exacerbate depressive and motor functions in PD by increasing the vulnerability of dopaminergic neurons to degeneration (Hemmerle et al., 2012).

4.4. Role of neuroinflammation

Emerging evidence suggests that inflammation is involved in the pathophysiology of depression in PD (Hall et al., 2018). Several other studies have found that inflammation, mediated by elevated proinflammatory molecules, plays an essential role in the comorbidity of depressive disorders and PD (Rocha et al., 2014). A cohort study of 52 PD patients with depression discovered a link between proinflammatory molecules and the development of cognitive decline and depression-like symptoms (Menza et al., 2010). A recent brief review also suggested the role of inflammation and immunomodulation in depression and cognitive impairment in PD patients (Pessoa Rocha et al., 2014). Inhibiting a proinflammatory cytokine, Tumor necrosis factor (TNF) reduced dopaminergic neuronal cell death and exerted neuromodulatory effects on depression-like symptoms and cognition disability in PD (McCoy et al., 2008). Another study showed a synergistic effect between inflammation and stress that induced microglial activation and proinflammatory cytokines, which induced depression-like symptoms and dopaminergic neuronal death in PD (de Pablos et al., 2014). Yet, another study found elevated proinflammatory levels resulted in non-motor symptoms like depression and fatigue in PD patients (Lindqvist et al., 2012). CSF levels of proinflammatory molecules and corticosterone were altered in patients with PD and major depression (Pålhagen et al., 2010). Other studies, too, have correlated blood serum proinflammatory cytokines with the development and magnitude of depression and anxiety in PD patients, albeit inconsistently (Wang et al., 2016). The proinflammatory cytokines possibly induce depressive-like disorders in PD patients by reducing 5-HT levels via an indoleamine-2, 3-dioxygenase (IDO) mediated reduction in levels of tryptophan hydroxylase, the rate-limiting enzyme for 5-HT biosynthesis (Haroon et al., 2012).

Recent research shed light on the possible mechanisms of the impact of the microbiota in the development, function and behavior of the brain. The leaky gut microbiota-mediated inflammatory responses have been related to the severity of depression-like symptoms in PD (Anderson et al., 2016). Other studies have also suggested a correlation between structural changes in gut microbiota and the development or manifestation of different neuropsychiatric conditions, including depression in PD (Li et al., 2017). Similarly, microbiota-gut-brain signaling has been implicated in non-motor symptoms, including depressive disorders in PD (Felice et al., 2016). A recent study found α-synuclein-immunoreactive inclusions in the enteric nervous system's submucosal and myenteric plexuses, indicating a possible gut-brain interaction that could result in the deposition of α-synuclein aggregates outside of the substantia nigra and the onset of non-motor symptoms, including depressive disorders in PD (Braak et al., 2006). Furthermore, a recent review suggested that stress directly influences the gut microbiome, increasing levels of proinflammatory cytokines that can exacerbate depressive disorders in PD patients (Galts et al., 2019).

4.5. Abnormal hippocampal neurogenesis

The development of non-motor functions, including depression, may not be directly related to the neuronal loss in the SNpc, but has also been associated with the hippocampal function (Lim et al., 2018). Hippocampal dysfunctions have been implicated in the development of non-motor functions, including depression and cognitive impairments in PD (Mishra et al., 2018). Various transgenic animal models with impaired hippocampal neurogenesis have exhibited depression-like phenotypes (Jürgenson et al., 2012). Recent reports suggest that reduced hippocampal and amygdala volumes were related to the development of depressive-like symptoms in PD patients (van Mierlo et al., 2015). According to a recent study, decreased volume in the hippocampus and amygdala was associated with depressive and anxiety symptoms in PD patients (Vriend et al., 2016). Reduced volume of CA2–CA3 in the Hippocampus was also reported in clinically newly diagnosed PD patients with depressive-like symptoms (Györfi et al., 2017). Another study found a significant inverse relationship between left hippocampal volume and the development of depressive-like symptoms in PD patients (Goto et al., 2018). Yet, another study found that depression in PD patients was associated with a weighted degree in the amygdala and para-hippocampal gyrus. (Zhang et al., 2019).

Additionally, in a recent study, depression-like symptoms were positively correlated with the grey matter volume in the right central gyrus in PD patients (Li et al., 2020c). In line with these observations, a recent study found that decreased amygdala and superior frontal gyrus functionality were linked to various non-motor functions, including depressive disorders in PD patients (Huang et al., 2020). In addition, antidepressant treatment has been reported to restore neuronal deficits, including hippocampal neurogenesis and depressive-like behaviors in PD patients (Bonato et al., 2018). Chronic stress decreases hippocampal neurogenesis, increases neuroinflammation, and alters autophagy pathology; it may be relevant in the hippocampal neurogenesis of PD patients with depression-like symptoms. Recent studies have suggested that dysregulations in autophagy and neuroinflammatory signaling may be regulatory mechanisms of abnormal hippocampal neurogenesis and depressive symptoms in PD (Lim et al., 2018).

4.6. Dysregulations in trophic support

Neurotrophic factors regulate neuronal plasticity and dopaminergic pathway in response to emotional stimuli. Disruptions in trophic support have also been linked to developing depressive-like disorders in PD (Rahmani et al., 2019). Brain-derived neurotrophic factor (BDNF), a neurotrophic factor, in particular, has been implicated in the etiology of depressive disorders and mediates the therapeutic response to antidepressants (Levy et al., 2018). The aberrant BDNF levels have also been linked to the etiology of PD, regardless of the comorbidity with depression (Rahmani et al., 2019). A recent finding suggested that decreased BDNF serum levels may be involved in developing depression-like symptoms in PD patients (Wang et al., 2017). Another recent study found that low BDNF serum levels distinguished between PD patients with and without depression and may reflect PD patients with depression (Huang et al., 2021). In addition, preclinical evidence suggests physical exercise alleviated depressive-like symptoms by modulating the decreased levels of BDNF in the striatum and hippocampus of the experimental PD model (Tuon et al., 2014). The combination of electroacupuncture therapy and medication ameliorated depressive symptoms in PD patients by significantly increasing the levels of BDNF (Xia et al., 2012). In another similar study, 6-OHDA-induced dopaminergic lesions and chronic pramipexole decreased the BDNF levels related to depressive-like symptoms in the rat model of PD (Berghauzen-Maciejewska et al., 2015). Val66Met, a gene polymorphism in the BDNF gene, has also been linked to impaired cognitive and motor function in PD patients (Cagni et al., 2017). BDNF activates downstream signaling pathways such as protein kinase (MAPK)–MEK and Akt–glycogen synthase kinase 3 (GSK3). As a result, genes encoding p11, a protein that transports 5-HT receptors to the cell surface, are transcribed. These downstream molecules of BDNF signaling have been linked to the aetiology of depression in PD (Dou et al., 2022). However, in contrast, a study reported that aberrant BDNF serum levels correlated with motor dysfunctions in PD irrespective of depressive and non-depressive symptoms (Scalzo et al., 2010). The role of Neuronal factors and signaling pathways in the implication of depression in PD is given in Fig. 3.

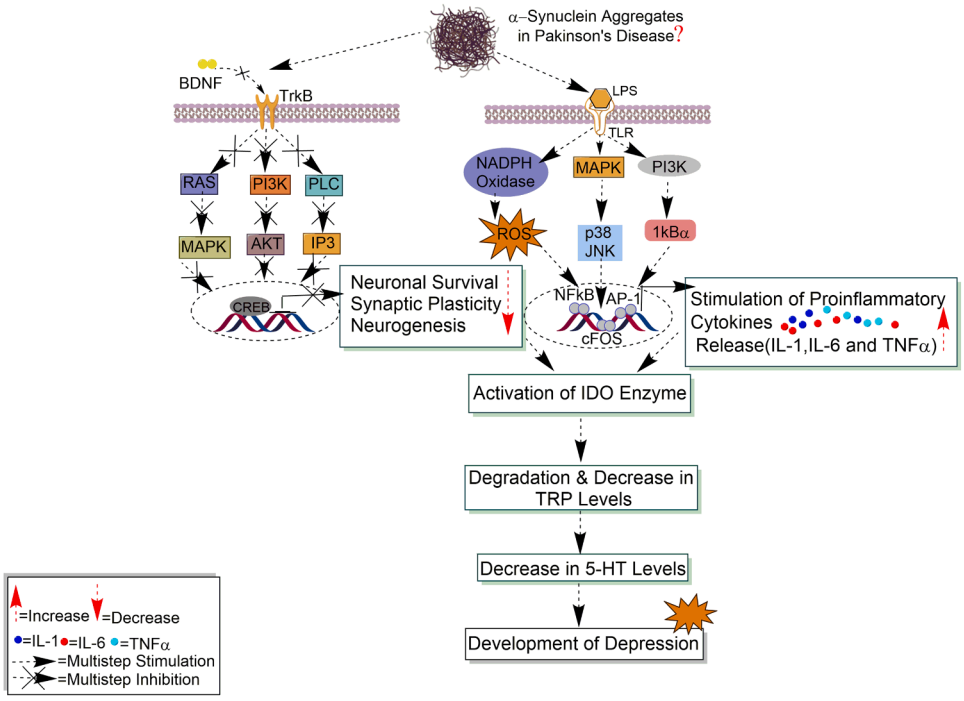

Fig. 3. Diagrammatic representation of the possible relationship between the onset of Parkinson's disease and the development of depression. Aggregation of α-synuclein may increase the risk of depression by negatively affecting the BDNF signaling and neuroinflammatory signaling pathways that lead to aberrant neurogenesis and synaptic plasticity process. Together these signaling pathways also result in the activation of the IDO enzyme, which breaks and degrades TRP, further resulting in a decrease in the levels of TRP. This increases the efficacy of some 5-HT receptors at the neuronal surface, thereby causing deficiency of 5-HT and the development of depression. Abbreviations: 5-HT, 5-Hydroxytryptamine; α-syn, α-synuclein; BDNF, Brain-derived neurotrophic factor; CREB, Cyclic AMP response element-binding protein; ERK, Extracellular signal-related kinase; IL1, Interleukin1; IL6, Interleukin 6; IDO, Indoleamine 2, 3-dioxygenase enzyme; IP3, Inositol trisphosphate; LPS, Lipopolysaccharide; MAPK, Mitogen-activated protein kinase; NADPH, Nicotinamide adenine dinucleotide phosphate hydrogen; NFκB, Nuclear factor κB; PKA, Protein kinase A; PI3K, Phosphoinositide 3-kinases; PLC, Phospholipase C; ROS, Reactive oxygen species; TLR, Toll-like receptor; TNF-α, Tumor necrosis factor-α; TrkB, Tropomyosin receptor kinase-B; TRP, Tryptophan.

4.7. Genetic factors

The relevance of genetic variables in the development of depressive-like disorders has also been debated. An increased risk of developing depressive-like symptoms and anxiety in PD patients suggests that depression and PD may share familial susceptibility factors (Hussein et al., 2021). A meta-analysis suggested a correlation between the serotonin-transporter-linked promoter region (5-HTTLPR) genotype (S/S-Allele) and an increased risk of developing depression in PD (Burn et al., 2006). A population-based cohort study reported an increased risk of several psychiatric disorders, including depression, in first-degree relatives of PD patients compared to first-degree relatives of controls (Arabia et al., 2007). Leucine-rich repeat kinase 2 (LRRK2) G2019S mutation in PD has also been related to the development of behavioral impairments, including depression and hallucinations (Belarbi et al., 2010). A revisited meta-analysis suggested that a functional variation in the 5-HTT gene could play a significant role in the metabolism of 5-HT and predispose it to the development of depression in PD (Karg et al., 2011). An exploratory study found that LC6A4 repeat and single-nucleotide polymorphisms were linked to an increased risk of developing depression-like symptoms in PD patients (Wang et al., 2019a; b). A recent study of 13 longitudinal cohorts found that alleles associated with PD risk, particularly GBA variants, are also linked to various motor and non-motor symptoms, including depression (Iwaki et al., 2019). The short allele of the 5-HTT gene has been associated with an increased risk of developing depressive disorders in PD patients (Galts et al., 2019). However, some studies have been very incontinent and did not suggest any association between genetic variation and the development of depression in PD (Gao and Gao, 2014). Therefore, more in-depth research is warranted to determine the impact of genetic factors in the manifesting depressive disorders in PD.

5. Treatment strategies for depression in PD

Depressive disorders in PD are diagnosed with high validity and specificity, which has improved the efficacy of psychotherapy and pharmacotherapy for treating depression in PD (Ho et al., 2021). The initial step for treating depression in PD needs assessment and optimal treatment of motor dysfunctions. The treatment approach should be multidimensional, with medications prescribed in various combinations based on the needs of the patients.

5.1. Pharmacological treatment

Antidepressants increase neuroplasticity and neurogenesis, making them promising therapeutic agents in the etiopathogenesis of depression in PD. At any given time, approximately 20–25% of PD patients with depression take antidepressants, most notably SSRIs (Weintraub and Mamikonyan, 2019). Despite its significant prevalence and implications, depression is treated only in 26% of PD patients (Galts et al., 2019). There have been relatively few controlled studies for treating depression in PD. Recent research indicates that antidepressants like tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and non-selective monoamine oxidase (MAO) inhibitors are all generally effective in the treatment of depressive disorders in PD (Ryan et al., 2019).

5.1.1. Tricyclic antidepressants

The use of TCAs in treating depression in PD patients shows some degree of efficacy, and in addition, they exhibit dopaminergic effects (Ray and Agarwal, 2020). The use of TCAs is limited due to typical adverse effects pertinent to PD patients like agitation, orthostatic hypotension and anticholinergic effects (Schneider et al., 2019). A randomized trial of antidepressants found that nortriptyline, a TCA, was efficacious in preventing depression in PD patients (Menza et al., 2009). Another TCA, desipramine, was effective against depression in PD patients in a randomized controlled study (Devos et al., 2008). A network meta-analysis, while comparing the efficacy and acceptability of antidepressants, concluded that TCAs might be the first choice of antidepressant treatment in PD (Liu et al., 2013). A review of case reports and case series suggests that TCAs like amoxapine, clomipramine, mianserin, and mirtazapine showed antidepressant and antipsychotic properties

(Sid-Otmane et al., 2020). Tertiary amine TCAs such as amitriptyline and imipramine have also demonstrated efficacy in treating depression in PD patients (Ryan et al., 2019). TCAs increase the activity of 5-HT, dopamine, and norepinephrine (NE) by blocking their reuptake, extending receptor sensitivity and increasing their levels in the synaptic cleft (Ryan et al., 2019). The elevated levels of 5-HT, dopamine, and NE in the synaptic cleft may likely contribute to their antidepressant effects in PD (Dorszewska et al., 2013).

Despite these promising results, the burden of adverse effects of TCAs is too high and overshadows the antidepressant properties they show. The TCAs induce adverse effects like excessive adrenergic stimulation, antihistaminergic, and anticholinergic activities by selectively binding to adrenergic (α1), histamine (H1) and muscarinic (M1) receptors, respectively (David and Gourion, 2016).

5.1.2. Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) show their antidepressant ability by inhibiting the reuptake of 5-HTT, thereby increasing serotonin levels in the synaptic cleft. Reports have suggested SSRI treatment to be more efficacious than placebo in treating depression in PD (Moonen et al., 2014). Multiple randomized controlled trials report that SSRI agents like citalopram, sertraline, paroxetine, and fluoxetine improved standardized depression-like symptoms in PD patients (Ryan et al., 2019). A 12-week randomized trial of buspirone, an SSRI, for depression-like disorders in PD showed efficacy with improvement in anxiety (Schneider et al., 2020). A review of case reports and case series also suggests that SSRIs like citalopram and escitalopram showed some improvement in depression-like symptoms in PD patients (Sid-Otmane et al., 2020). Various open-label trials have reported use of SSRIs for depression in PD had convincing results and good tolerability (Weintraub and Mamikonyan, 2019). Some trial case reports have suggested that SSRIs treatment for depression worsens motor dysfunctions in PD; however, most studies could not replicate and substantiate it (Ryan et al., 2019). Studies suggest that there is a higher density of 5-HT receptors in depressed patients resulting in a decrease in the levels of 5-HT, which are implicated in the pathophysiology of depression (Steinberg et al., 2019). Several other studies have also found elevated 5-HTT levels and subsequent decreased levels of 5-HT in PD patients (Politis et al., 2010). SSRIs are, therefore, also found to be effective in alleviating depressive symptoms in PD patients by inhibiting the reuptake of 5-HT in the synaptic cleft (Tan et al., 2011). The antidepressant effect of SSRIs in PD may be due to their ability to selectively bind to 5-HT and increase serotonin levels in the somatodendritic region of serotonergic neurons, desensitizing 5-HT-1A receptors resulting in the neuronal impulse flow and increased release of 5-HT from axonal terminals (Tan et al., 2011). In general, SSRIs are safer and better tolerated than TCAs and have been tolerable during the treatment of depression in PD (Schrag and Taddei, 2017).

5.1.3. Serotonin-norepinephrine reuptake inhibitors

SNRIs are reported to increase levels of 5-HT and NE in the synaptic cleft, thereby alleviating depression-like symptoms in PD (Dallé and Mabandla, 2018). Similar to SSRIs, SNRIs alleviate depressive symptoms in PD patients by inhibiting the reuptake of 5-HT in the synaptic cleft (Dale et al., 2015). Reports suggest that NE dysregulations are implicated in the pathogenesis of PD (LeWitt, 2012). Furthermore, decreased NE transporter binding in the locus coeruleus has been correlated with depression in PD patients (Jaunarajs et al., 2011). Dopamine is also related to reward and motivation; studies suggest that impaired dopamine release has also been implicated in the pathophysiology of depression in PD patients or in general (Blonder et al., 2013). Reports also suggest that SNRIs at higher doses inhibit the reuptake of dopamine receptors, thereby increasing dopamine levels and alleviating depressive symptoms (Li et al., 2020a). Similarly, SNRIs inhibit the reuptake of NE and increase the NE levels in the synaptic cleft, thereby decreasing depressive symptoms in PD patients (Nishijima et al., 2017). Because of their relatively favorable safety profile and tolerance and the lack of evident side effects, SNRI drugs are utilized to treat depression in PD (Ryan et al., 2019). Reports suggest that SNRIs are a substitute for depression in PD with inadequate response to SSRIs (Takahashi et al., 2005). In a controlled trial of antidepressants in PD, Atomoxetine, an SNRI, was not efficacious for depression in PD patients but improved cognitive disorders (Menza et al., 2009). In a randomized controlled trial, venlafaxine was quite effective in treating depressive disorders in PD patients (Richard et al., 2012). Duloxetine, an SNRI, was very well tolerated and valuable in treating depression in PD patients in an open-label experiment (Bonuccelli et al., 2012). These observations are corroborated by another open-label trial study, where duloxetine improved mood and motor functions in PD (Nishijima et al., 2017).

5.1.4. Monoamine oxidase inhibitors

MAOI drugs also have antidepressant characteristics in PD patients by altering the amounts of 5-HT, NE, and dopamine in the synaptic cleft (Youdim, 2018). Reports suggest that MAO inhibitors like phenelzine and tranylcypromine show effective results against depressive-like symptoms in PD (Thomas et al., 2015). Because of its effect on dopamine levels, MAO inhibitors such as rasagiline and selegiline are used to treat motor symptoms of PD (Naoi et al., 2020). These observations are in line with a placebo-controlled trial study, where rasagiline treatment significantly decreased depressive-like symptoms and improved motor dysfunctions in newly diagnosed PD patients (Korchounov et al., 2012). Reports also suggest that selegiline does not pose substantial side effects or mortality for depression patients with PD (Frisina et al., 2008). MAO inhibitors are used to treat depressive-like symptoms in treatment-refractory depression (TRD), partial response or non-response to two complete trials of any antidepressants at selected therapeutic doses over a long time (Serafini et al., 2018). Other studies report that selegiline showed antidepressant properties and improved motor function in PD patients (Shulman et al., 2013). Selegiline also significantly improves depression and motor functions in PD patients already being treated with antidepressant and antiparkinsonian agents (Youdim and Bakhle, 2006). Studies suggest that dysfunction in the monoaminergic neurotransmission is a risk factor for depression in PD (Prange et al., 2022). MAOIs inhibit the metabolism of 5-HT, NE and dopamine by the inhibition of enzymatic conversion into their corresponding metabolites, thereby increasing their levels inside the brain (Özdemir et al., 2021). Therefore, MAOIs increase the levels of 5-HT, NE and dopamine by preventing their oxidative deamination and increasing their association with their respective transporters, which may alleviate non-motor symptoms including depressive symptoms in PD (Özdemir et al., 2021).

5.1.5. Other antidepressant agents

Other antidepressants that act on dopamine, opioid or neuropeptide receptors may also be useful owing to the neurobiology of PD and depression (Tizabi et al., 2019). Bupropion is an atypical antidepressant primarily used to treat PD-mediated depression and/or depressive disorders caused by PD treatments by inhibiting the reuptake of NE and dopamine (Załuska and Dyduch, 2011). Bupropion may act on dopaminergic and noradrenergic systems, inhibit the reuptake of NE and dopamine, and prevent loss of dopamine and noradrenaline innervation in the limbic system, thereby decreasing depressive symptoms in PD (Buddhala et al., 2015). Recently a scoping review also emphasized the clinical use of Bupropion in PD patients with comorbid depressive symptoms (Vismara et al., 2022). In another study, amfebutamone (Bupropion) also showed promising efficacy in treating the motor functions of PD patients (Załuska and Dyduch, 2011). Likewise, some more antidepressants, captopril and perindopril, showed antidepressant properties in Parkinsonism, likely by influencing serotonin levels (Perez-Lloret et al., 2017). In a randomized controlled study Pramipexole, a dopamine agonist, improved depression symptoms in patients with PD mainly by exhibiting a direct antidepressant effect (Barone et al., 2010). Pramipexole showed an antidepressant effect in a mouse model of PD via

the dopamine D3 receptor (Wei et al., 2021). Pramipexole treatment alleviates depression-like symptoms and motor dysfunction in PD patients with depression in a meta-analysis of randomized controlled trials (Jiang et al., 2021). Pramipexole, a presynaptic dopamine receptor agonist, shows an affinity for dopamine D3 and α2-adrenergic receptors and may increase` nigrostriatal dopaminergic transmission by activating dopamine D2 receptors, thereby improving the clinical symptoms, including depressive symptoms in PD (Jiang et al., 2021). Similarly, ropinirole medication has been shown to alleviate both motor and non-motor functions in PD patients (Nashatizadeh et al., 2009). In a prospective multicenter study, ropinirole improved non-motor symptoms, including depression, in PD patients (Rektorova et al., 2008). Ropinirole alleviates depressive symptoms in PD patients probably by upregulating the expressions of dopamine receptor D3 (Lian et al., 2019). The most common and efficacious drug for treating motor dysfunctions in PD is L-3, 4-dihydroxyphenylalanine (L-DOPA). L-DOPA has been attributed to alleviate some mood disorders in PD patients (Jaunarajs et al., 2011). It is a dopamine precursor that can easily penetrate the blood-brain barrier, replenish dopamine levels inside the brain, and likely lessen the depression-like symptoms in PD patients (Galts et al., 2019).

5.2. Non-pharmacological treatment

5.2.1. Electroconvulsive therapy

Electroconvulsive therapy (ECT) is an effective treatment strategy for treating depressive disorders in PD or depression in general (Borisovskaya et al., 2016). ECT is commonly used to treat TRD in which depressive illnesses do not respond to antidepressant medication (Williams et al., 2017). ECT significantly alleviated PD patients' motor functioning in randomized controlled research, 9 prospective observational studies, and 4 retrospective investigations (Takamiya et al., 2021). A systematic review of about 43 articles suggested that in ECT, 93% of PD patients improved their depressive disorders (Borisovskaya et al., 2016). Bitemporal ECT significantly ameliorated depression-like symptoms in 78-year-old woman PD patients (Bailine et al., 2008). Surprisingly, ECT alleviated depressive-like symptoms in PD patients following subthalamic nucleus (STN) transcranial magnetic stimulation (TMS) surgery (Chou et al., 2005). ECT was also effective in improving psychosis-like behavior in PD patients regardless of the comorbidity of depression (Ueda et al., 2010). While ECT may improve depression-like disorders in PD patients, it may make them more susceptible to delirium, an acute confused state (Tsujii et al., 2019). Recently a pilot determined that ECT was also effective against bradykinesia and immobility in depressed patients (Powell et al., 2020). Reports suggest that ECT specifically improves motor functions by increasing dopaminergic transmission by enhancing dopamine type 1 receptor binding (Volkaerts et al., 2020). ECT-induced amelioration of motor symptoms may be responsible for improving depressive disorders in PD (Takamiya et al., 2021). Reports also suggest that ECT positively affects the noradrenergic and serotonergic transmission, which may play a key role in alleviating depression symptoms in PD or general (Murayama et al., 2021). ECT may also show an antidepressant effect in PD because it mediates neuronal plasticity by mediating the interactions between mGluR1/5 and AMPA receptors that may increase synaptic potentiation in the prefrontal cortex (Ruan and Yao, 2021).

5.2.2. Transcranial magnetic stimulation

TMS is a non-invasive magnetic stimulation of the prefrontal cerebral cortex using magnetic and electrical energy to treat depression-like conditions (Borisovskaya et al., 2016). Prolonged exposure to higher frequency-TMS, frequency higher than 1 Hz or low-frequency TMS, and frequency lower than 1 Hz alters cortical excitability producing significant neurophysiological changes in patients with various neurological and psychiatric disorders (Lefaucheur et al., 2014). Studies investigating the role of TMS in the dorsolateral prefrontal cortex reported that TMS was effective in improving depression scores in PD patients in a randomized, double-blind, placebo-controlled study (Pal et al., 2010). In a meta-analysis of randomized controlled clinical trials, repetitive TMS clinically modulated depression-like conditions in PD patients (Xie et al., 2015). In another meta-analysis, repetitive TCM improved depression-like symptoms similar to SSRI treatment (Hai-Jiao et al., 2020). According to a PRISMA-compliant meta-analysis, repeated TSM has significant therapeutic effects on motor and non-motor functioning in patients with PD (Li et al., 2020b).

More randomized controlled trials show that repetitive TMS alleviated depression and motor symptoms in PD patients for at least a short period (Chen et al., 2021). A recent randomized sham-controlled trial suggested that TMS over the primary motor cortex (M1) and dorsolateral prefrontal cortex alleviated motor dysfunctions and depressive symptoms in PD patients (Kar, 2022). Studies suggest that TMS induces stimulation of the left dorsolateral prefrontal cortex, including hypo-metabolic prefrontal areas, dorsal and ventromedial prefrontal cortex, perirhinal and orbitofrontal cortex, amygdala, insula, and precuneus that have been implicated in the depression symptomology (Baeken and De Raedt, 2022). Most studies direct TMS to the dorsolateral prefrontal cortex, which is involved in cognitive function and emotional responsiveness (Kuehne et al., 2015). TMS has also been reported to influence the levels of neurochemical factors like 5-HT, BDNF and glutamate that are involved in the etiopathogenesis of depression (Zhou et al., 2019a). These observations suggest that depressive symptoms in PD may be alleviated by TMS-induced stimulation of the left dorsolateral prefrontal cortex, thereby improving cerebral blood circulation, catecholamine metabolism and releasing endogenous dopamine levels (Zhou et al., 2019a). TMS may thus be a viable treatment option for depressive symptoms in PD.

5.2.3. Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is a type of psychological treatment used to treat depressive disorders and psychosis that do not respond to other interventions (Dobkin et al., 2020b). CBT may be employed as a first-line or supplementary therapeutic technique in PD patients with mild-to-moderate depressive-like symptoms (Marsh, 2013). CBT was a feasible and helpful approach for treating depression in PD in a randomized controlled trial (Dobkin et al., 2011b). A pilot study Recent case studies and open trials have found that CBT significantly improves depression symptoms in PD patients (Reynolds et al., 2020). In a randomized controlled trial, CBT improved various depressive-like symptoms in PD (Tizabi et al., 2019). Another randomized, controlled trial suggested that CBT may be a viable approach for treating depression-like symptoms in PD patients (Dobkin et al., 2011a). A pilot study also suggested the feasibility of CBT for treating anxiety and depression in patients with PD (Calleo et al., 2015). A study reported that CBT improved the quality of life in PD patients with depression by improving social skills, perceived emotional well-being and somatic motor functions (Hadinia et al., 2017). According to a comprehensive review, CBT reduces anxiety and depression-like symptoms and may help in treating depressive-like disorders in PD or in general (Zhang et al., 2020). A recent pilot study by Telehealth Mindfulness showed that CBT was feasible and effective for depression in PD (Interian et al., 2022). Reports suggest that CBT improves awareness, helps developing a better understanding of emotions and negative appraisals which helps improve skills for coping with PD-associated functional impairment (Khatri et al., 2020). CBT activates the prefrontal cortex including the ventrolateral prefrontal cortex and dorsolateral prefrontal cortex, which are responsible for regulating emotions, thereby, enhancing the cognitive control network activity in depression (Yang et al., 2018). CBT helps mediate left cortical activation, left hemisphere balance and subcortical activation, which are at least partly associated with the pathophysiology of movement disorders like PD (Berardelli et al., 2015). The observations suggest that PD patients with depression, if subjected to CBT, may show more reduction in depression scores from the baseline than those

who do not and can therefore be a promising treatment strategy against depression in PD patients.

5.2.4. Physical exercise

Physical exercise is another effective strategy that reduces anxiety and depressive disorders in PD. Studies extolling the benefits of exercise for depression in PD patients are primarily related to improvement in motor functions (Jin et al., 2020). A systematic review of the impact of physical activity on depression in PD patients reported that exercise might assuage the dysfunctions of motor function and depressive disorders in PD patients (Wu et al., 2017). In randomized clinical trials of the last decade, physical exercise improved cognitive function, sustained attention and mental flexibility in PD patients suffering from depressive disorders (da Silva et al., 2018). In a randomized controlled pilot study, qigong exercise decreased depression scores and improved motor functions in PD patients (Schmitz-Hübsch et al., 2006). In a recent randomized clinical trial, physical exercises like yoga, stretching and resistance training reduced anxiety and depression-like symptoms of spiritual well-being in PD patients (Kwok et al., 2019). During multimodal exercise programs, aerobic physical exercise helped people improve cognitive and behavior impairments in PD patients (Tanaka et al., 2009). A systematic evaluation of prospective studies found that physical activity generally delayed the onset of depression in PD patients (Mammen and Faulkner, 2013). Furthermore, a pilot, single-blind, randomized controlled experiment found that treadmill training enhanced cognitive and motor abilities in PD patients (Picelli et al., 2016). A systematic review highlighted how physical activity significantly improved non-motor symptoms like depression in PD patients (Cusso et al., 2016). A study reported that physical inactivity was related to developing depressive symptoms and cognitive dysfunction in PD patients (van Nimwegen et al., 2011). Reports suggest that physical activities, particularly aerobic exercise, regulate neurochemistry and neuroplasticity of the brain by upregulating the levels of neurotrophins like BDNF and NGF (Liang et al., 2021). BDNF and NGF have been reported to regulate dopamine levels, branching and remodeling of axons and dendrites, as well as intracellular calcium levels, thereby improving synaptic connections and serotonergic system functioning, which may help in impeding the PD progression and depression (Liang et al., 2021). Studies also suggest that physical exercise attenuates basal ganglia hyper excitability by improving the dopaminergic and glutamatergic neurotransmission in PD (Reynolds et al., 2016). Aerobic exercise in rats has been reported to increase dopamine synthesis in the nigrostriatal pathway (Foley and Fleshner, 2008). Additionally, a preliminary study on humans suggests that aerobic physical exercise increased dopaminergic signaling and reduced postural instability during the early stages of PD (Fisher et al., 2013). Also, physical exercise has modulatory effects on nondopaminergic signaling, including serotonergic and GABA-ergic signaling, which is relevant to depression (DeBoer et al., 2012). Physical exercise has been associated with the increase in the release of β-endorphins which regulate specific types of motor function that have important implications in determining the pathophysiology of specific depressive symptoms (Tabikh et al., 2021). Physical exercise, thus, could act on these nondopaminergic systems to improve non-motor symptoms like depression, more specifically during the early stages of PD. These observations imply that PD patients need to exercise to alleviate the depression symptoms. The possible role of pharmacological and non-pharmacological treatments for depressed PD patients is given in Fig. 4.

6. Conclusions and future directions

PD is a common neurodegenerative disease, and many depression-like symptoms appear to be regularly associated with PD complicating its course and progression. The incidence of depression symptoms in PD takes into consideration the various study settings and diagnostic techniques. The neurobiological pathways and related mechanisms involved in developing depression in PD indicate a correlative pathophysiologic substrate. Depression in PD patients is multidimensional and has a detrimental impact on health and quality of life by increasing or exacerbating motor dysfunctions and morbidity. Therefore, careful interventions, multi-stepped-care approaches and multiple medication trials, including psychotherapy using standard validated measurements and clinical judgment, may be required to decrease the depression symptoms and severity of the disease. Despite research indicating that psychological symptoms are also core aspects of PD and may significantly influence functioning and quality of life, therapeutic techniques remain suboptimal. The need for better intervention is further reflected by the failure of standard antidepressant therapies to prevent comorbid conditions. Dysregulations in neurotransmitters, diminished trophic support, HPA axis disruptions, neuroinflammation and excitotoxicity,

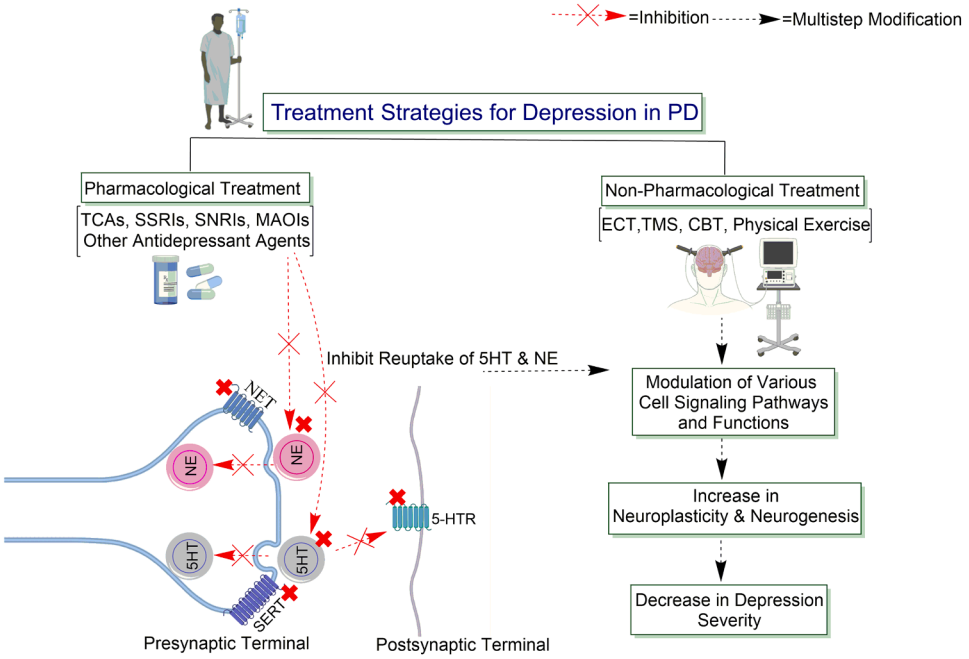

Fig. 4. Pharmacological and non-pharmacological treatments for depressed Parkinson's Disease patients increase noradrenergic or serotonergic neurotransmission by blocking the NE or 5HT transporter at presynaptic terminals (NET, SERT), producing long-lasting changes in monoaminergic neurotransmission. The inhibition of the reuptake of 5HT and NE may enhance the neurotransmission, presumably by prolonging the dwell-time of the transmitters in the synapse. The sustained signaling via NE or 5HT increases the expression of specific downstream cell signaling pathways and functions, thereby increasing neuroplasticity and neurogenesis. Abbreviations: 5HT, 5-hydroxytryptamine; 5-HTR, 5-hydroxytryptamine receptor; CBT, Cognitive-behavioral therapy; ECT, Electroconvulsive therapy; MAOIs, Monoamine oxidase inhibitors; NE, norepinephrine; NET, norepinephrine transporter; SSRIs, Selective serotonin reuptake inhibitors; SNRIs, Serotonin-norepinephrine reuptake inhibitors; SERT, serotonin transporter; TCAs, Tricyclic Antidepressants; TMS, Transcranial magnetic stimulation.

are the possible underlying neurobiological mechanisms for depression in PD. Therefore, newer therapeutic approaches targeting these molecular mechanisms need to be better elucidated that may alleviate the comorbidity of depression in PD patients. As previously noted, diagnosing depression in PD is difficult due to the difficulty in distinguishing between psychological symptoms of depression and motor functions of PD (e.g., bradykinesia); it is, therefore, important to minimize dopaminergic treatments while concomitantly employing non-pharmacologic approaches. If the depressive symptoms persist and only get worse with the progression of the PD, pharmacological interventions become paramount and even adjunctive or monotherapy may also be considered. The scope of the studies regarding symptoms and severity of depression in PD should be broad, with a larger pool of potential subjects and more refined exclusive inclusion criteria. The biomarkers for diagnosing depression in PD need to be emphasized, which may help develop an understanding of the underlying molecular mechanism of depression in PD and develop better, safer and more efficacious treatment cocktails. Double-blind prospective clinical trials need to determine the safety, efficacy, and adverse consequences of the treatments involved. An individualized multimodal treatment approach employing psychotherapeutic intervention and pharmacologic intervention should be considered. Each study should thoroughly estimate the severity of motor symptoms using a validated scale like the Unified Parkinson's disease rating scale (UPDRS) and the severity of depression symptoms using a validated scale such as the HAM-D. Every treated patient should have detailed documentation of all previous therapy trials and reactions. Early diagnosis, appropriate treatments, better study design, and more comparative studies may substantially improve PD severity and quality of life. Additionally, noncontrolled studies have reported that cognitive-behavioral and interpersonal psychotherapy may improve depression-like symptoms in PD patients. A wide variety of different methods are currently in clinical trials, but more preclinical and clinical studies are needed to evaluate their efficacy and tolerability for depression in PD patients. At the moment, the treatments for depressive disorders in PD show suboptimal results, and those that showed promising results in animal models have failed to show any significant efficacy in clinical studies. Therefore, more randomized, double-blind, placebo-controlled studies are warranted.

CRediT authorship contribution statement

Mir Hilal Ahmad: Conceptualization, Writing – original draft, Writing – review & editing. **Moshahid Alam Rizvi:** Writing – review & editing. **Mansoor Ali:** Writing – review & editing. **Amal Chandra Mondal:** Conceptualization, Writing – original draft, review and final editing.

Declaration of Conflict of Interest

None.

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