



Depression in Patients with Parkinson's Disease: Current Understanding of its Neurobiology and Implications for Treatment

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Abstract

Depression is one of the most frequent and burdensome non-motor symptoms in Parkinson's disease (PD), across all stages. Even when its severity is mild, PD depression has a great impact on quality of life for these patients and their caregivers. Accordingly, accurate diagnosis, supported by validated scales, identification of risk factors, and recognition of motor and non-motor symptoms comorbid to depression are critical to understanding the neurobiology of depression, which in turn determines the effectiveness of dopaminergic drugs, antidepressants and non-pharmacological interventions. Recent advances using in vivo functional and structural imaging demonstrate that PD depression is underpinned by dysfunction of limbic networks and monoaminergic systems, depending on the stage of PD and its associated symptoms, including apathy, anxiety, rapid eye movement sleep behavior disorder (RBD), cognitive impairment and dementia. In particular, the evolution of serotonergic, noradrenergic, and dopaminergic dysfunction and abnormalities of limbic circuits across time, involving the anterior cingulate and orbitofrontal cortices, amygdala, thalamus and ventral striatum, help to delineate the variable expression of depression in patients with prodromal, early and advanced PD. Evidence is accumulating to support the use of dual serotonin and noradrenaline reuptake inhibitors (desipramine, nortriptyline, venlafaxine) in patients with PD and moderate to severe depression, while selective serotonin reuptake inhibitors, repetitive transcranial magnetic stimulation and cognitive behavioral therapy may also be considered. In all patients, recent findings advocate that optimization of dopamine replacement therapy and evaluation of deep brain stimulation of the subthalamic nucleus to improve motor symptoms represents an important first step, in addition to physical activity. Overall, this review indicates that increasing understanding of neurobiological changes help to implement a roadmap of tailored interventions for patients with PD and depression, depending on the stage and comorbid symptoms underlying PD subtypes and their prognosis.

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Key Points

Depression is highly prevalent in Parkinson's disease (PD) across all stages of the disease, depending on dynamic neurobiological changes related to dysfunction of limbic networks and monoaminergic systems across time.

Motor and non-motor symptoms (in particular apathy, anxiety, rapid eye movement sleep behavior disorder and cognitive impairment) comorbid to PD depression are critical to delineate the neurobiology of PD depression.

In vivo functional imaging supports the effectiveness of dopaminergic and serotonergic treatments in PD depression and helps develop a roadmap for tailored therapeutic interventions according to PD subtypes and disease stage.

1 Introduction

Non-motor symptoms are well-recognized as a major source of disability for patients with Parkinson's disease (PD), which may exceed the burden related to motor impairment [1, 2]. Moreover, treatment of non-motor symptoms is often difficult and may either improve or worsen under dopaminergic replacement therapy used to alleviate motor symptoms. In particular, neuropsychiatric non-motor symptoms may severely alter the quality of life of both patients and their caregivers [3–5], and possibly even more during the coronavirus disease 2019 (COVID-19) pandemic [6]. Among these, depression is recognized as one of the most frequent and disabling conditions, alongside anxiety, fatigue and pain, affecting one-quarter of patients at PD onset [7], but which may occur at any stage of PD, including the prodromal stage [1, 4, 8, 9], and may shorten life expectancy [10].

Depression in patients with PD is mostly characterized by loss of pleasure/enjoyment, including dissatisfaction and loss of appetite, but less feelings of guilt, self-hate, and loss of libido [11], although fundamental supporting criteria are not different from those of depressive or anxiety disorders in the general population [12].

Symptoms related to depression were among the most frequent non-motor symptoms in patients with PD using the Non-Motor Symptoms Scale (NMSS) and highly correlated to lower quality of life across all stages [1, 9, 13]. The prevalence of depression in PD is high [14], but variable, depending on the stage of the disease and patients' comorbidities, suggesting that depression may have different pathophysiological determinants and be related to specific PD subtypes [15]. Overall, the interaction of depression heralding PD and incidental depression after the diagnosis of PD is complex and a unified pathophysiological model of depression in PD is lacking. In addition, pathophysiological changes involved in the pathogenesis of PD (including neurotransmission abnormalities of the dopaminergic, serotonergic, noradrenergic or cholinergic systems, dysfunction of striato-thalamo-cortical circuits, frontal and limbic cortical structural and functional alterations, inflammation, and mitochondrial dysfunction) are also suspected to play a prominent role for depression in the general population, in addition to neuroendocrine changes, as reviewed previously [16, 17].

We followed a pragmatic literature search strategy using PubMed with the Medical Subject Heading (MeSH) terms 'parkinson disease' in the title and 'depression' combined with 'prevalence', 'incidence', 'longitudinal', 'MRI', 'SPECT', 'PET', 'trial', 'therapy' and 'treatment', yielding 1031 results. In addition, we queried the Cochrane library database of systematic reviews for treatments, yielding two relevant occurrences [18, 19] and the Movement

Disorders Society Evidence-Based Medicine Reviews, with two relevant reviews [20, 21].

This review aims to help bridge the gap between novel hypotheses regarding the pathophysiology of depression in PD and the available and promising therapeutic interventions, and thereby promote accurate treatment of depression, which remains under-recognized and insufficiently treated.

2 Epidemiology and Clinical Characteristics of Depression in Parkinson's Disease (PD)

2.1 Prevalence

Depression in PD is recognized as one of the most frequent and disabling non-motor symptoms. Prevalence estimates of depression are wide, ranging from 2.7 to 90% [14], depending on the evaluation and diagnostic criteria, patients' characteristics and comorbidities, and stage of the disease. Overall, clinically significant depression is present in 35% [14, 22, 23], up to 40.4% for outpatients with PD and 54.3% for inpatients with PD, albeit with variable severity [24, 25]. Major depressive disorder in PD is found in about 20% [14, 26–28]. Risk of depression is considered four times higher than in the general population matched for age, sex and comorbidities [29].

Importantly, depression is found at any stage of PD. Recently, data obtained in a large population indicated that 38% of patients are treated or diagnosed for depression within the year following diagnosis [30], consistent with other studies in de novo patients [8, 31]. Depression is found in up to 70% of mid-to-advanced PD outpatients without dementia [4], and associated with other neuropsychiatric symptoms [32]. In addition, prevalence, severity and symptoms of depression were similar in patients with mid-to-advanced PD and in patients with essential tremor and (mostly focal) dystonia [33].

Importantly, depression in PD may be underdiagnosed and important manifestations, including fatigue, sleep disorders and weight changes, may be directly attributed to PD and not to depression complicating PD [34]. The reverse also stands true as initial PD motor (amimia, slowness) and non-motor symptoms may be interpreted as manifestations of depression, instead of PD, leading to erroneous treatment [35].

Furthermore, the sensitivity and specificity of recommended diagnostic tools remains variable [36–40], although the Geriatric Depression Scale (GDS-15), Beck Depression Inventory-I (BDI-I/1a), and Montgomery-Åsberg Depression Rating Scale (MADRS) are considered valid scales to measure depression severity [27], in line with previous guidelines [38].

In addition, screening of depression is a critical step and can also be performed using the BDI, MADRS and GDS thanks to their high-sensitivity in patients with PD [38]. In particular, the 15-item version of the GDS represents a time-efficient screening tool, as it is easily comprehensible and incorporates relatively few somatic-related items overlapping with the core symptoms of PD (sleep disturbances, alteration of facial expression, slowness), which may falsely inflate depression scores [38].

Overall, few symptoms are specific to PD depression in comparison with depression in the general population, and patients with PD may often experience clinically significant symptoms although they may not fulfill criteria for major depressive disorders [14, 27].

Overall, the burden of depression in PD related to both its prevalence and repercussions advocate for an 'inclusive' approach in which somatic symptoms are equally considered as part of PD depression for screening and severity scores to avoid underdiagnosis and undertreatment (see below) [41, 42]. However, although challenging, the distinction between depression and apathy has critical implications for treatment [21, 44], underpinned by specific limbic dysfunction [43, 45], and should be operated using dedicated scales [36, 38] such as the Lille Apathy Rating Scale (LARS) [46] or Starkstein Apathy Scale [39]. This is further emphasized in the Neurobiology and Treatment sections.

2.2 Incidence and Risk Factors

Longitudinal studies are particularly valuable to decipher the dynamics of depression across PD stages and identify clusters of patients with distinct demographic and clinical characteristics, which may inform the etiopathogenesis of PD-related motor and non-motor symptoms [47].

Data from clinical trials indicate that incidental depression occurs in about 16% of *de novo* patients newly diagnosed with PD and previously free of depression, in addition to the 13.8% of patients already suffering from depression at diagnosis [13, 48]. Overall, the incidence rate of depression in newly diagnosed patients is increased twofold in comparison with age-matched non-PD patients [49], and up to 10 times higher than in the general population aged over 50 years. Female sex is consistently regarded as a risk factor for depression in PD [23, 49–51] and in the general population [52]. Contrastingly, influence of age at onset is highly dependent on the setting [50, 53–56], although patients with depression after diagnosis may be older [57, 58]. Furthermore, non PD-specific risk factors (age, female sex, personal history of anxiety or depression, family history of depression, worse functioning on activities of daily living, and worse cognitive status) have been shown to be three times more influential for PD depression than PD-specific risk factors (longer disease duration, more severe motor symptoms

and use of levodopa) [59, 60]. Moreover, personalized prediction of depression using machine learning confirms the influence of non-PD-specific predictors (depression and anxiety severity, presence of rapid eye movement sleep behavior disorder [RBD] and history of depression) in addition to PD-specific factors (age at onset and duration) [56]. In particular, evidence that RBD represents an important risk factor for depression in PD is accumulating [61].

Overall, a systematic review identified that autonomic symptoms, motor fluctuations, severity and frequency of symptoms, staging of the disease, and PD onset and duration were associated with the presence of depression and anxiety in patients with PD [62]. However, one should not dismiss that personal and familial psychosocial and environmental factors also play an important role in the dynamics and repercussions of PD depression [42], which all influence the coping strategies of patients and their caregivers depending on age and stage [63].

2.3 Association Between Depression and Motor Symptoms

Greater motor and global impairment, closely related to worse quality of life, is a constant finding in depressed patients [28, 48, 64–66], although the impact of depression on motor impairment is modest [48, 67–69]. In addition, depression in early PD is regarded as a risk factor for worse motor and global prognosis [64, 70, 71]. This is also the case in patients with advanced PD and persistent depression [72]. This is consistent with previous studies confirming the association between depression and PD severity (PD duration, Hoehn and Yahr and Unified Parkinson's Disease Rating Scale (UPDRS) scores, motor complications, duration of treatment) such as the DEPAR and DoPaMiP surveys in older and more advanced patients, including those with mild cognitive impairment [50, 73, 74]. Furthermore, worse motor prognosis was found in mid-stage patients with greater depression, apathy and anxiety as well as greater cognitive impairment [75]. Importantly, comorbid depression over time is not related to worse motor prognosis in prospective studies [64] but may accelerate the initiation of dopaminergic replacement therapy in early PD [48].

Higher depression scores were found in patients with motor fluctuations and/or dyskinesia [68, 76, 77], also in comparison with drug-naïve patients [78]. Greater dyskinesia, levodopa equivalent dose and impulse control disorders were also associated with depression [66, 79, 80]. In addition, greater severity of depression was the strongest predictor of impulse control disorders of all types, independently of treatment with dopamine agonists [81].

Association with specific motor subtypes is unclear and may reflect unstable classification in early PD [82]. Depression prevalence was similar in Postural Instability and Gait Disorder (PIGD) versus tremor-dominant (TD) patients in

early [13], and across, PD stages [83] but its severity was greater in non-TD de novo patients [31] and early PIGD-dominant patients [84]. Furthermore, mild depression was significantly associated with gait impairment in early PD [85] and axial symptoms may be associated with greater prevalence and severity of depression across PD stages [28, 68, 69, 73, 86–88], especially in those with rapid progression with or without cognitive impairment [89]. This association is also found for anxiety [90]. Moreover, there is no definitive association between depression and the side of greatest motor impairment [59, 91, 92], similar to anxiety [90], although (mild) depression may be more severe in patients with bilateral symptoms [84].

2.4 Association Between Depression and Other Non-Motor Symptoms

The association of depression with other neuropsychiatric non-motor symptoms is particularly frequent in PD, which is considered as indirect evidence of co-occurring, and possibly intricately linked or synergistic pathophysiological mechanisms.

Anxiety is long recognized as one of the most frequent comorbid conditions accompanying depression [4, 93–96], although both conditions may exist on their own [4, 73, 90, 97]. As such, risk factors are partly distinct in depression with or without anxiety, and, in particular, anxiety may be more frequent in patients aged < 60 years at diagnosis, and be related to motor fluctuations [86, 90, 98]. Furthermore, the prevalence of depressive disorder is greater in patients with non-specific anxiety subtypes [98]. In addition, anxiety is an important risk factor when considering incident depression, besides insomnia [93]. Apathy is also frequently associated with depression, leading to consider a hypodopaminergic neuropsychiatric triad consisting of apathy, depression and anxiety in PD [99]. However, association of depression on one side, with apathy and anxiety on the other side, is complex, as symptoms most frequently co-exist [100], although they also occur in isolation [101–103], which may indicate overlapping and also distinct pathophysiological mechanisms related to distinct prognostic outcomes [44, 99].

Interestingly, earlier studies suggested a link between cognitive impairment and depression in older patients and those with long PD duration [23, 74, 76, 77, 104–106]. More precisely, many studies demonstrated a strong association between depression and anxiety and worse executive or multiple domain cognitive functioning [107–111]. In addition, lower education level was also associated with depression in PD [68, 112, 113]. Psychosis in patients with early PD also predicted greater prevalence of depression and anxiety, in addition to greater cognitive impairment, and worse

prognosis over 2 years [114]. Overall, depression and cognitive impairment share many common risk factors [31, 115].

Recent studies show that depression may herald dementia in PD and across other neurodegenerative disorders [116]. Depression and anxiety were found to be the strongest predictors of the longitudinal decline in verbal and visual learning performance in PD [117], as well as in old-age depression in the general population [118]. Analysis in the Parkinson's Progression Markers Initiative (PPMI) cohort showed that patients with early PD and depression had an almost twofold risk to develop mild cognitive impairment within 4 years [119]. In addition, patients with the more severe depressive symptoms experience greater and more rapid decrease of performance in critical cognitive tasks (processing speed, verbal learning and verbal delayed recall) [120]. Interestingly, poorer multi-domain cognitive performance predicts increased incidence of depression and anxiety in early PD [121, 122]. In addition, cognitive decline is also related to incidental depression in mid-stage patients [123]. Moreover, specific association of apathy with subsequent cognitive impairment or dementia was also demonstrated in non-depressed patients [124]. As such, depression, apathy and anxiety, represent risk factors of cognitive impairment and dementia, whereas risk and domain-specific cognitive impairment restricted to one of these three neuropsychiatric conditions remains inconclusive [109, 117, 120, 125, 126]. Overall, evidence is strong to support that depression related to cognitive impairment and dementia represents a different nosologic entity from depression in de novo and prodromal patients with PD, and is underpinned by distinct, possibly more widespread, pathological burden.

Most interestingly, it was recently pointed out that patients with RBD in early PD had greater worsening of depression over time, also associated with worse motor and non-motor prognosis and death, in a large cohort [127]. Overall, patients with RBD have more severe depression and may represent a PD subtype with faster motor progression and cognitive decline [128], possibly related to the extent of amyloid pathology [129].

Recent mediation analyses indicate that longitudinal changes in autonomic dysfunction and depressive symptoms are linked [130, 131], with greater depression in those with more severe autonomic dysfunction [132]. Association of constipation and depression was also found [66, 133]. Interestingly, earlier development of autonomic dysfunction was demonstrated to predict more rapid progression in PD and death, although neuropathological findings assessing the burden of Lewy bodies were similar [134]. Depression is also more severe in patients with pain [135, 136]. Furthermore, greater severity of depression was found to better predict dysphonia than global motor impairment [137]. Depression, as well as anxiety, also predicts greater insomnia in early PD [138].

2.5 Course of Depression

Longitudinal follow-up in prospective studies and the PPMI cohort provide new insight in the variable course of depression, in particular in early PD [28, 104, 139]. Importantly, in early PD, depressive symptoms resolved in one-third [28, 123] to one-half of patients, especially for younger patients and those with milder symptoms [139]. Similarly, in de novo patients with PD, depression was half less frequent 2 years after diagnosis, following the initiation of dopamine replacement therapy [140]. However, one has to keep in mind that the role of dopaminergic and antidepressant treatments remains complex to disentangle in observational studies, and that clinical factors may both influence the natural history of PD depression and the response to treatments. In particular, risk factors for depression (female sex, age and PD duration) are associated with a lower likelihood that depressive symptoms resolve [123, 139]. In addition, greater cognitive decline and worsening of UPDRS part II were associated with the worsening of depression score over 30 months in mid-stage patients [123]. However, further research is needed to identify the factors that predict favorable evolution and good response to treatments of PD depression at the individual level and may be applicable in the clinical context. Notably, longitudinal positron emission tomography (PET) imaging studies have the potential to identify compensatory mechanisms, possibly involving the serotonergic system [141] and related to the improvement of apathy in early PD [43].

2.6 Depression in Prodromal PD

Depression represents one of the earliest and most frequent alerting symptom across age-related neurodegenerative disorders. Prospective historical cohort studies using registry and medical records showed that history of depression is about twice more frequent at the time of PD diagnosis compared with age-matched controls (9.2% vs. 4%) [142–144] and multiplies the risk to be diagnosed with PD by at least twofold [145, 146]. Meta-analysis regarding risk factors for PD confirmed that the odds ratio (OR) for mood disorders was 1.86 (95 % confidence interval [CI] 1.64–2.11), behind familial history of PD, constipation and absence of smoking [147]. Interestingly, association of depression and anxiety was associated with the highest risk (OR 2.4, 95 % CI 1.2–4.8), and lag time might be higher for anxiety [144]. Overall, depression may precede motor symptoms by 5 years or more [148] and the risk for depression in premotor patients is regularly increasing until PD diagnosis [142, 144, 148]. Interestingly, all patients with major depressive disorder who developed PD within 10 years were characterized by the triad consisting in mild asymmetric motor slowing,

idiopathic hyposmia and substantia nigra hyperechogenicity [149]. Moreover, it was recently demonstrated that patients with depression following PD diagnosis were older and had a twofold risk of dementia in comparison with patients with prediagnostic depression [57].

2.7 Depression in Genetic PD

Whether genetic forms of PD predispose to depression remains an open question, although monogenic forms of PD resembling idiopathic PD with Lewy-body synucleinopathy represent critical etiopathogenic models.

Depression is frequent in patients with genetic PD [150–152], although depression was not related to mutations of parkin, leucine-rich repeat kinase 2 (LRRK2) and apolipoprotein E (APOE) status in a large study gathering 632 families [153]. In addition, a recent study showed that depression severity was similar to healthy controls in both LRRK2 and glucocerebrosidase (GBA) mutation carriers at risk of PD as well as RBD and impulse control disorders [154]. Nevertheless, prevalence of depression is close to 30% in LRRK2 patients with manifest PD and may predate motor symptoms, similar to patients with idiopathic PD [155, 156], whereas prevalence of dementia might be lower [156–158]. Moreover, depression severity increased over 2 years in heterozygous carriers of GBA mutations, who are at high risk of PD, also associated with greater olfactory and cognitive impairment [159], and depending on the alleles [157].

Several studies indicate that there are no associations between depression in PD and known genetic polymorphisms of the serotonin and dopamine transporter genes [160, 161]. However, other studies are positive for the short allele of the serotonin transporter (SERT) gene-linked polymorphic region [162, 163], but not for the monoamine oxidase (MAO)-A gene promoter-associated polymorphism [163]. Interestingly, PD depression is associated with polymorphism of the cannabinoid 1 receptor (CB1) gene [164], which is of interest since cannabinoid CB1 receptors likely modulate the excitability of dorsal raphe neurons [165].

Overall, these robust statistical associations and temporal precedence suggest that depression and PD may share common pathophysiological mechanisms (Table 1), and that association with specific comorbidities and risks factors may reflect different pathological routes [15, 166, 167].

3 Neurobiology of Depression

Understanding the pathophysiological mechanisms and the respective importance of dopaminergic versus non-dopaminergic pathology underlying depression in patients with PD is critical to address the heterogeneity of PD depression and develop tailored interventions to treat depression

at all stages. In vivo structural and functional imaging have greatly improved our understanding of changes related to PD depression and dysfunction of corticostriatal circuits [44].

In particular, the role of monoamine deficits related to depression has long been investigated in PD, which is characterized by multiple and progressive monoaminergic and catecholaminergic dysfunction, largely extending beyond the core nigrostriatal dopaminergic degeneration. Indeed, it is now established that serotonergic and noradrenergic deficits occur in prodromal patients with RBD [168, 169] and in A53T mutation carriers of the alpha-synuclein (SNCA) gene [170], and are prominent in de novo patients with idiopathic PD [171]. Moreover, postmortem histopathological staging suggests that monoaminergic deficit might be sequential, starting with noradrenergic and serotonergic dysfunction heralding nigrostriatal dopaminergic dysfunction in prodromal patients, and progressively extending to cholinergic and neocortical dysfunction, based on the topography of Lewy-body synucleinopathy [172], although this may apply to a subset of patients and remains controversial [173–176]. In addition, depression is more severe in patients with akinetic-rigid, bilateral and axial symptoms (see Sect. 2.3) and correlated to bradykinesia [28, 69, 177, 178], suggesting greater dopaminergic injury possibly involving the motor nigrostriatal system, but also more widespread, and extrastriatal pathology associated with axial symptoms. Overall, evidence accumulates to support that PD depression is causally related to pathological mechanisms starting in the prodromal state and that progression of dopaminergic and non-dopaminergic pathology over the PD course may explain the variable expression and outcome of depression over time (Fig. 1).

3.1 Neurotransmission Abnormalities

3.1.1 Dopamine Imaging

The increased prevalence and incidence of depression in PD and its association with greater motor impairment and bradykinesia suggest that dopaminergic denervation may play an important role for depression. In particular, dysfunction of

the presynaptic terminals of the mesolimbic dopaminergic system has been demonstrated using single photon emission computed tomography (SPECT) and PET imaging across PD stages (Fig. 1).

Indeed, decreased binding of [¹¹C]RTI-32, a PET ligand for the dopamine (DAT) and noradrenaline (NERT) transporters, was demonstrated in the (left) ventral striatum in patients with PD and more severe depression, next to noradrenergic dysfunction in other limbic structures [179]. In addition, decreased DAT correlating with depression severity was found in the left anterior putamen using (99m) Tc-TRODAT-1 [180], and in the bilateral striatum and putamen [181], thalamus [182, 183], right caudate [184] and left cingulate cortex [185] using [123I]FP-CIT-SPECT. Interestingly, decreased DAT in the left caudate in PD and left putamen in primary dystonia correlated with greater depression [186]. Decreased dopaminergic metabolism was also demonstrated in the bilateral putamen and caudate nucleus proportional to PD depression severity [187]. Furthermore, striatal decrease of DAT labeling is also found in de novo apathetic patients with PD [188] and in non-PD patients with major depressive disorder [189].

On the contrary, other studies have rather found greater DAT labeling in the bilateral striatum, left caudate and right putamen in depressed patients in comparison with non-depressed patients with PD, including patients taking antidepressants [190, 191], or no dopaminergic striatal change related to depression using [18F]FP-CIT PET [192].

Overall, DAT imaging provides evidence for presynaptic dopaminergic system dysfunction related to PD depression, either via a reduced (i.e. greater degeneration) or increased availability (possibly leading to abnormal dopamine clearance) of such a transporter.

In addition, disequilibrium of D3 versus D2 receptors has been shown to be related to not only depression severity but also to motor impairment in the ventral striatum and pallidum [193]. Indeed, a lower [¹¹C]-(+)-PHNO (D3-specific) to [¹¹C]raclopride (D2/3 non-specific) BP_{ND} ratio was observed in the striatum in depressed drug-naïve patients, possibly as a result of preferential downregulation of postsynaptic D3 receptors.

Table 1 Summary of epidemiological findings for depression in patients with Parkinson's disease

PD depression is highly prevalent across all PD stages, including prodromal and de novo PD patients
Non-PD-specific risk factors (older age, female sex, personal or familial history of depression) are three times more influential than PD-specific risk factors for depression
Greater global and motor impairment is associated with PD depression
Apathy, anxiety, and cognitive impairment are frequently associated with PD depression. Use of validated scales is helpful to distinguish these symptoms
Depression may herald dementia, likely related to widespread extrastriatal and non-dopaminergic pathology
PD depression is often persistent, although depression may resolve in 33% of patients in early PD

PD Parkinson's disease

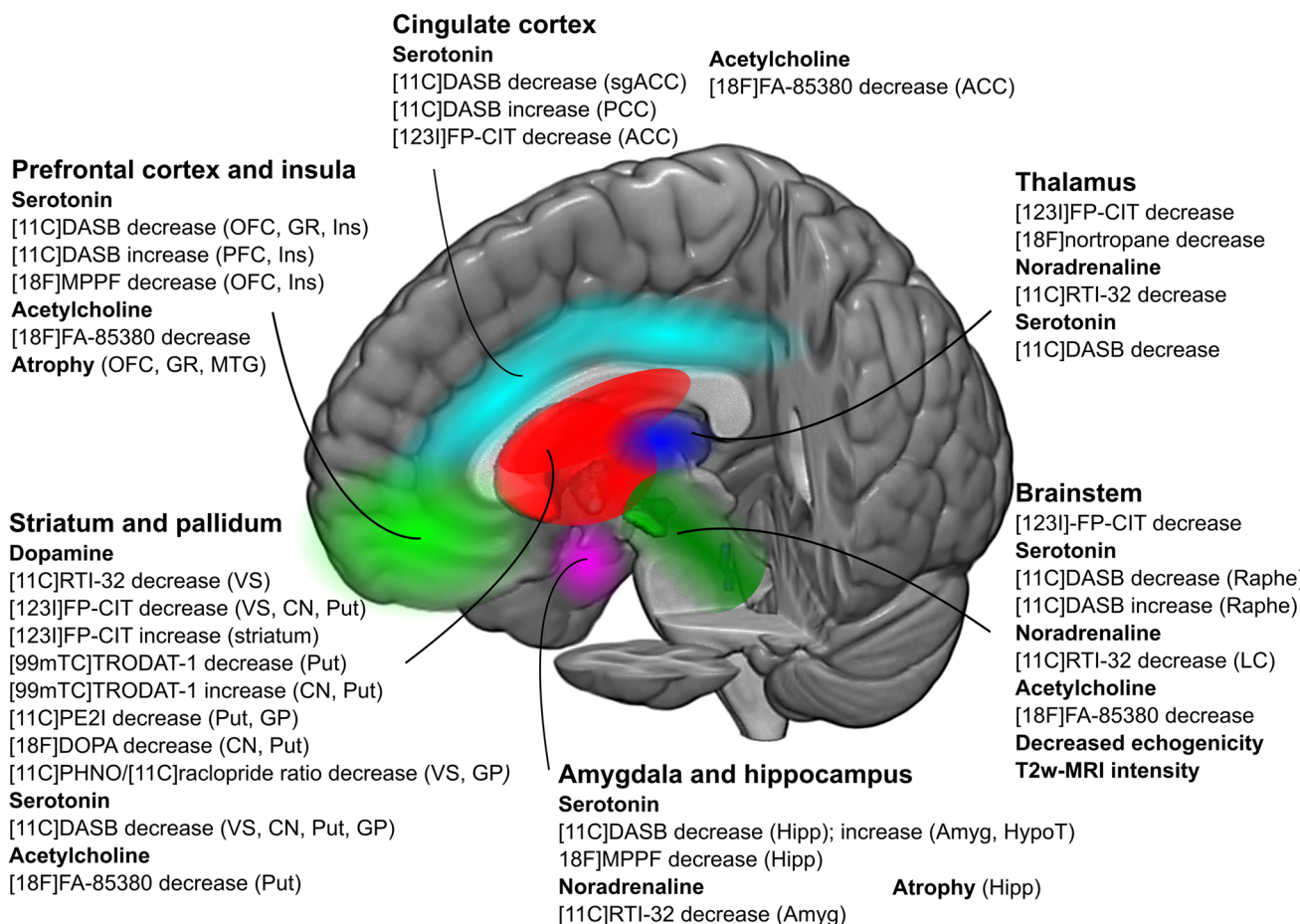


Fig. 1 Structural and functional abnormalities related to depression in Parkinson's disease (red: striatum; light green: prefrontal cortex and insula; green: brainstem; light blue: cingulate cortex; blue: thalamus; violet: amygdala and hippocampus). ACC anterior cingulate cortex, sgACC subgenual ACC, Amyg amygdala, CN caudate nucleus, GP

globus pallidus, GR gyrus rectus, Hipp hippocampus, HypoT hypothalamus, Ins insula, LC locus coeruleus, MTG medial temporal gyrus, OFC orbito-frontal cortex, PCC posterior cingulate cortex, PFC prefrontal cortex, Put putamen, VS ventral striatum

Overall, these studies pinpoint the role of mesolimbic dopaminergic denervation in PD depression, although small sample sizes in PET and SPECT studies, use of different tracers, and custom methods of analysis may limit the comparison of these findings.

3.1.2 Serotonin Imaging

SPECT studies suggested a relationship between depression in PD and decreased [123I]FP-CIT binding in the dorsal midbrain, classically considered to reflect binding to the SERT [182, 194]; however such association was not found in the large PPMI cohort [195]. Using [11C]DASB, a highly specific PET radiotracer for SERT, it was demonstrated that depression was associated with an increased binding in the caudal raphe nuclei, amygdala, hypothalamus, and posterior cingulate cortex [196]. Furthermore, such an increase positively correlated to depression severity in the prefrontal and cingulate cortex, insula and putamen in antidepressant-naive

patients with PD [197], possibly reflecting upregulation of SERT, in turn resulting in greater serotonin clearance. Contrastingly, depression in de novo, drug-naïve patients with apathy, depression and anxiety was associated with decreased [11C]DASB in the limbic system and greater severity specifically correlated to greater serotonergic dysfunction in the bilateral subgenual anterior cingulate cortex (ACC) [171]. Moreover, greater serotonergic pathology related to depression was recently demonstrated across PD stages, underlying the major influence of serotonergic dysfunction in limbic corticostriatal circuits [198], which may specifically underpin microstructural alterations in the caudate nucleus [45]. Regarding postsynaptic dysfunction, patients with PD depression had lower binding of [18F]MPPF to the 5HT1A receptor in the left hippocampus, right insula, left superior temporal cortex, and the orbitofrontal cortex [199]. Decreased echogenicity of the basal limbic midbrain was also found in patients with PD depression

using transcranial sonography, as well as alterations of signal intensity and relaxation time of the pontomesencephalic midline structures using T2-weighted magnetic resonance imaging (MRI) [200–202].

3.1.3 Noradrenaline Imaging

Studies investigating noradrenergic involvement in PD depression are scarce. However, using [11C]RTI-32 PET imaging, an *in vivo* marker of both the dopamine and noradrenaline transporters, noradrenergic dysfunction related to PD depression and anxiety was found in the bilateral locus coeruleus and thalamus as well as the right amygdala [179]. Overall, widespread noradrenergic dysfunction was recently evidenced in PD using [11C]-MeNER PET imaging, in association with decreased neuromelanin in the locus coeruleus [203]. Most interestingly, noradrenergic injury was greater in parkinsonian patients with RBD, who also had greater cognitive impairment, slowed EEG activity, and orthostatic hypotension in comparison with patients without RBD [203], which may be related to depression [61, 93].

3.1.4 Cholinergic Imaging

The role of cholinergic cortical deficit in PD dementia is well established [204]. Furthermore, striatal and limbic cholinergic dysfunction were also demonstrated in patients with axial or gait disorders [205] and RBD [206]. As such, cortical cholinergic loss was also related to depression score in mid-stage demented and non-demented male patients with PD [207]. In addition, decrease of 2-[18F]FA-85380 binding to $\alpha 4\beta 2$ -nicotinic receptors was prominent in the anterior cingulate cortex and frontoparietal cortex related to PD depression, in addition to the left putamen, left midbrain, and occipital cortex [208], partly overlapping with cognitive impairment. Interestingly, progression of cholinergic deficit has been found to spare the prefrontal cortex in early PD, and subsequently follow an anterior-to-posterior prefrontal degeneration gradient, which may relate to progressive cognitive impairment and comorbid depression [209].

3.2 Structural and Metabolic Abnormalities

Limbic and striatal atrophy were consistently demonstrated in PD depression, associated with widespread dysfunction of the limbic network. In particular, depression severity was correlated to lower grey matter density in the bilateral orbitofrontal, bilateral rectal gyrus, right medial temporal gyrus, anterior and medial cingulate gyrus, and parahippocampal gyrus [210], left hippocampus and right parahippocampal gyrus [211], in addition to white matter loss in the anterior cingulate bundle and the inferior orbitofrontal region [212].

This is consistent with earlier studies indicating hypometabolism in the anterior cingulate cortex and medial frontal and orbitofrontal cortex [213–215], whereas hypermetabolism is present in the amygdala [216], which is preserved from atrophy [217].

In addition, recent diffusion-weighted imaging studies showed decreased fractional anisotropy in the anterior cingulate bundles [218] and other limbic association tracts in the left [219, 220] and right [45] hemispheres. Specifically, microstructural alterations of the inferior longitudinal fasciculus were consistently associated with PD depression and cognitive impairment, as well as RBD, olfactory impairment and systemic inflammation [221]. In addition, functional connectivity between the striatum, thalamus and limbic frontotemporal regions [222, 223] is altered in depressed patients as well as between the amygdala and frontoparietal regions [217]. Notably, functional connectivity in the posterior cingulate cortex was increased in patients with PD depression and was negatively correlated to the severity of depression [224], in line with recent findings [225]. As such, differences mainly involving the functional connectivity of the posterior cingulate cortex and insula with the amygdala, hippocampus, precuneus and frontal cortex may help to classify patients with or without PD depression diagnosed with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [225], although further research is needed to validate imaging biomarkers of PD depression in independent and larger cohorts. Overall, the importance of the anterior and subgenual cingulate cortex is paramount, as previously evidenced [226]. Moreover, greater white matter injury is found in PD depression and is associated with cognitive impairment and gait disorders [227]. Finally, patients with Lewy body disorders and depression had greater synucleinopathy in the substantia nigra, ventral tegmental area and nucleus accumbens, whereas beta-amyloid and hyperphosphorylated tau burden was similar in patients with or without depression [228].

3.3 Inflammation

Inflammation is one of the mechanisms of neurodegeneration, first suggested by the presence of activated microglial cells in the substantia nigra pars compacta and elevated levels of proinflammatory cytokines in the brain and blood of patients with PD [229]. Regarding PD depression, elevated levels of the soluble interleukin-2 receptor (sIL-2R) and tumor necrosis factor- α (TNF α) [230], as well as C-reactive protein (CRP) [231], were reported. Most importantly, elevated CRP was associated with decreased connectivity between the ventral striatum and ventromedial prefrontal cortex, correlated to greater anhedonia in non-PD patients with major depressive disorders [232]. In addition, dysregulation of genes involved in signaling pathways related

to the immune system and metabolism present in patients with depression, including the nicotinamide phosphoribosyltransferase (NAMPT) for lipid and glucose regulation, was recently demonstrated in early untreated patients with PD, using transcriptomic meta-analysis and network analysis of blood microarrays [233]. Furthermore, inflammation is critical in changes of the microbiome, which may also be involved in PD depression [234].

4 Treatment

The consequences of depression, even when its severity is mild, are dramatic and overwhelming, acting negatively on global well-being, quality of life, physical activity, health-care burden and family equilibrium [60, 235]. Notably, the evidence base for treating depression has grown substantially in the latest decade, including randomized clinical trials of non-pharmacological interventions and meta-analysis of pharmacological treatments [18, 21, 236–238]. Randomized placebo-controlled trials of serotonin and noradrenaline reuptake inhibitors are presented in Table 2, in addition to the most recent studies not previously reviewed [18, 21]. Importantly, several factors may explain that treatment of depression in PD may still be delayed, insufficient, or even absent, especially if severity is mild [48, 73, 83, 239]. Indeed, underrecognition of depression in PD remains problematic, as manifestations of depression are intermingled with multiple comorbid motor and non-motor symptoms. Moreover, depression may resolve over time in up to one-third of patients with PD, in line with a strong placebo effect in randomized clinical trials [240, 241], where intensive medical follow-up and coping strategies may help, as observed for apathy [242]. Retrospective analysis of registry data shows that trend of diagnosis and treatment of depression in the first year following PD diagnosis slightly decreased from the years 2000 to 2015 [30]. Citalopram, amitriptyline, fluoxetine and mirtazapine were the most frequent pharmacological treatments used in recent years [30]. However, use of pharmaceutical and non-pharmaceutical interventions is increasingly supported by the pathophysiological mechanisms described in Sect. 3 of this review and help develop a roadmap of tailored interventions for patients with PD and depression, depending on the stage and comorbid symptoms (Fig. 2).

4.1 Dopaminergic Treatments

Optimal motor control is critical and should be finely tuned with oral dopamine replacement therapy using levodopa or dopamine agonists as a first step (Fig. 2) [21]. Importantly, a positive effect on PD depression was demonstrated for levodopa (DoPaMiP [73]) and the dopamine agonist

pramipexole [243], while ropinirole [244, 245], rotigotine [246] and MAO-B inhibitors deserve further investigation [20, 21, 247]. In particular, a direct antidepressant effect (rather than mediated by the improvement of motor symptoms) of pramipexole (a highly potent D3-agonist) on depressive symptoms across PD stages was demonstrated in a multicentric, large-scale, randomized, placebo-controlled trial over 12 weeks [243], in line with earlier studies [248]. Notably, 25% of patients also received antidepressant drugs. In addition, a randomized clinical trial indicated significantly higher recovery (60.6% vs. 27.3%) for pramipexole versus sertraline (50 mg/day) [249], although sertraline was also effective [250].

In addition, piribedil, a potent D2/3 agonist, highly effective to treat apathy following subthalamic nucleus deep brain stimulation (STN-DBS) was also shown to improve depression [251]. Contrastingly, trait anxiety improved in de novo patients using low-dose rotigotine compared with placebo, whereas apathy and depression improved but similarly in the rotigotine and placebo groups, stressing the importance of care, follow-up and placebo effects [242].

Furthermore, enhancement of dopaminergic transmission using the selective MAO-B inhibitor rasagiline was not found to be superior to placebo on PD depression in a randomized controlled trial [252], although previous evidence indicated that rasagiline may improve mood [253] and depression in combination with antidepressants [254], with a low risk for adverse serotonin syndrome. However, safinamide, a reversible MAO-B inhibitor and GABAergic modulator, improved depressive symptoms in addition to the expected improvement of motor fluctuations [255]. Moreover, there is growing evidence that continuous infusion therapies using levodopa/carbidopa intestinal gel or subcutaneous apomorphine may also improve depressive symptoms [256–258], in addition to their important benefits on motor symptoms and quality of life [259–262]. Moreover, results from the open-label, randomized INSIGHTS study evaluating the efficacy of levodopa infusion on non-motor symptoms are awaited [261]. Overall, treatment should be optimized to achieve the best control of motor and non-motor fluctuations in the first instance [21, 258], considering STN-DBS or infusion therapies as appropriate (Fig. 2).

4.2 Serotonergic, Noradrenergic, and Cholinergic Treatments

As in non-PD depression, selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) are considered effective and well tolerated (Table 2). Effectiveness of antidepressants in PD depression was confirmed in the three largest randomized clinical trials with 48, 52 and 115 non-demented patients with PD and major depressive

Table 2 Randomized placebo-controlled trials and recent studies of serotonergic and noradrenergic pharmacological treatments of depression in patients with Parkinson's disease

Study	Design	Treatment	Comparator	Trial duration	Diagnostic criteria	Treatment group	Outcome	Findings	Safety
Wermuth et al., 1998 [241]	Double-blind RCT, multicentric	Citalopram 10–20 mg/day	Placebo, n = 19	52 weeks	DSM-IIIIR MDD and HAM-D-17 ≥ 13	N = 18, age 65.9 years [44–79]	HAMD-17	No significant difference vs. placebo	High discontinuation rate in both groups in the continuation phase. Dry mouth, heart rate, nausea
Leenijens et al., 2003 [240]	Double-blind RCT, multicentric	Sertraline 50–100 mg/day	Placebo, n = 6	10 weeks	DSM-IV MDD	N = 6, age 67 years (7.8)	MADRS	No significant difference vs. placebo	Not reported
Devos et al., 2008 [263]	Double-blind, 3-arm RCT, monocentric	Desipramine 75 mg/day	Placebo, n = 16	30 days	DSM-IV MDD and MADRS ≥ 20	N = 17, age 63 years [57–65] MADRS 29 [27, 34]	MADRS	Significant decrease at days 14 and 30; greater than placebo	OH (1); mild AE twice as frequent as in placebo and citalopram
Menza et al., 2009 [264]	Double-blind, 3-arm RCT, monocentric	Citalopram 20 mg/day	Placebo, n = 17	8 weeks	DSM-IV MDD	N = 15, age 57 years [56–64] MADRS 25 [24, 28]	HAMD-17	Significant decrease at day 30; greater than placebo	Bradykinesia (1); erectile dysfunction (1)
Weintraub et al., 2010 [271]	Double-blind RCT, monocentric	Paroxetine CR 12.5–37.5 mg/day Atomoxetine 80 mg/day	Placebo, n = 27	8 weeks	IDS-C ≥ 22	N = 17, age 62.9 years (9.3)	IDS-C	Significant decrease, greater than placebo	Dry mouth 41%, constipation 35%, OH 12%, insomnia 12%, dizziness 12%
Richard et al., 2012 [265]	Double-blind, 3-arm RCT, multicentric	Paroxetine 40 mg/day Venlafaxine XR 225 mg/day	Placebo, n = 39	12 weeks	DSM-IV and HAM-D-17 > 12	N = 18, age 62.8 years (8.1) N = 28, age 63.8 years (9.5); IDC-S: 35.1 (7.3), GDS: 9.4 (2.9) N = 42, age 65.2 years (9.8); MADRS 21.0 (6.8)	HAMD-17	No significant difference vs. placebo; 22.7% vs. 9.5% response rate	Constipation 25.9%, insomnia 14.8%
								Significant decrease; greater than placebo (–6.2, 95% CI –2.2 to –10.3)	AE 86%, sexual dysfunction 23.8%, fatigue 21.4%, somnolence 19.1%, tremor 16.7%, dizziness 16.7%, constipation 14.3%, headache 14.3%
								Significant decrease; greater than placebo (–4.2, 95% CI –0.1 to –8.4)	AE 87%, sexual dysfunction 23.5%, headache 23.5%, somnolence 23.5%, insomnia 20.6%, constipation 20.6%

Table 2 (continued)

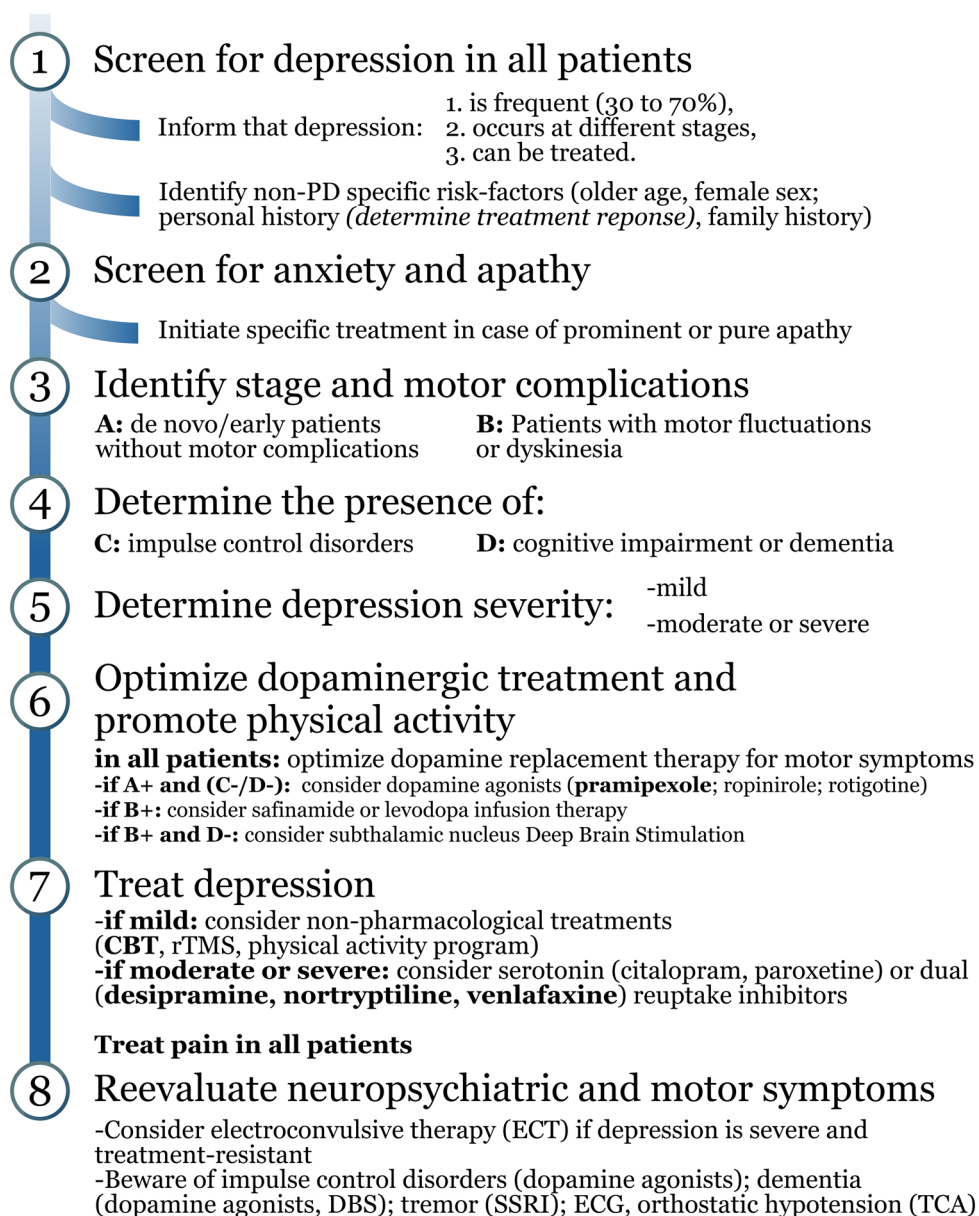
Study	Design	Treatment	Comparator	Trial duration	Diagnostic criteria	Treatment group	Outcome	Findings	Safety
Takahashi et al., 2019 [272]	Open-label, randomized trial, multicentric	Paroxetine 10–25 mg/day Escitalopram 10 mg/day	None	10 weeks	QIDS-J ≥ 6	<i>N</i> = 25; age 70.3 years (8.4) QIDS-J: 11.3 (4.0)	QIDS-J	Significant decrease [–2.4 (3.6)]	AE 36%; gastrointestinal
Meloni et al., 2020 [273]	Double-blind, randomized trial, monocentric	Duloxetine 20–40 mg/d 5-hydroxytryptophan 50 mg/day	Placebo, <i>n</i> = 23 (crossover)	4 weeks	HDRS ≥ 14 and BDI-II ≥ 7	<i>N</i> = 27; age 72.4 years (8.4) QIDS-J: 10.9 (4.1) <i>N</i> = 23, age 67.61 years (6.55)	HDRS-21	Significant decrease [–2.3 (3.9)] Significant decrease at weeks 4, 8, 12, and 16; greater than placebo	AE 37%; dyskinesia (1), tremor (2) Not reported
DeKarske et al., 2020 [276]	Open-label, phase II trial, multicentric	Pimavanserin 34 mg/day, monotherapy Pimavanserin 34 mg/day, add-on (SSRI/SNRI)	None	8 weeks	HAMD-17 ≥ 15	<i>N</i> = 21 HAMD-17: 19.1 (2.1) <i>N</i> = 24 HAMD-17: 19.2 (3.8)	HAMD-17	Significant decrease [–11.2 (0.99)] Significant decrease [–10.2 (0.78)]	Gastrointestinal 14.9%, psychiatric 14.9%

Average, standard deviation (using parentheses) or range (using brackets) are indicated for age, depression scores, and study findings. Adverse events are given as a percentage or number (using parentheses) as available

Treatments in bold are those determined as efficacious or likely efficacious in the MDS evidence-based medicine review for the treatment of non-motor symptoms in PD [21]

AE adverse event, *BDI-II* Beck Depression Inventory-II, *CR* controlled-release, *DSM-IV/RR MDD* Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised criteria for major depressive disorders, *DSM-IV MDD* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depressive disorders, *GDS* Geriatric Depression Scale, *HAMD-17* Hamilton Depression Scale–17-item version, *HDRS* Hamilton Depression Rating Scale 21-item version, *IDS-C* Inventory for Depressive Symptomatology–Clinician Rated, *MADRS* Montgomery–Åsberg Depression Rating Scale, *MDS* Movement Disorder Society, *OH* orthostatic hypotension, *QIDS-J* Quick Inventory of Depressive Symptomatology–Japanese, *RCT* randomized controlled trial, *SNRI* serotonin and noradrenaline reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *XR* extended release

Fig. 2 Suggested roadmap for the diagnosis and treatment of depression in patients with PD. Treatments in bold are those determined as efficacious or likely efficacious in the MDS evidence-based medicine review for the treatment of non-motor symptoms in PD [21]. *CBT* cognitive behavioral therapy, *DBS* deep brain stimulation, *ECG* electrocardiogram, *ECT* electroconvulsive therapy, *PD* Parkinson's disease, *rTMS* repetitive transcranial magnetic stimulation, *SNRI* serotonin and noradrenaline reuptake inhibitor, *TCA* tricyclic antidepressant



disorder, respectively [263–265]. These trials demonstrated the short-term efficacy of both desipramine and citalopram within 4 weeks [263], of nortryptiline versus paroxetine and placebo within 8 weeks [264], and of both paroxetine and venlafaxine versus placebo over 12 weeks [265]. Moreover, superiority of dual (nortryptiline, amitriptyline, venlafaxine) or predominantly noradrenergic (desipramine) reuptake inhibitors was suggested, in line with earlier trials [250, 266–268] and confirmed using network analysis [269]. In particular, desipramine had a more rapid efficacy compared with citalopram, possibly mediated by the effect on lassitude, inability to feel, apparent sadness, and concentration difficulties, although mild adverse effects were twice as frequent [263], related to anticholinergic effects in particular. Overall, initiation of TCAs requires special

attention and should be carefully evaluated in patients with orthostatic hypotension and those with cardiovascular diseases or family history of sudden death, cardiac dysrhythmia or conduction defects. To date, insufficient evidence is available to support the clinical use of other noradrenergic agents, including reboxetine [270], atomoxetine [271] and duloxetine [272]. Administration of 5-hydroxytryptophan (50 mg) over 4 weeks, the precursor of serotonin synthesis, may also ameliorate PD depression, but not apathy, as demonstrated in a recent single-center, randomized, placebo-controlled crossover trial in 25 patients [273]. One has to keep in mind that contrary to dopaminergic treatments, SSRIs may, in rare cases, aggravate motor symptoms [274], notably tremor [263]. A pilot randomized trial suggested that 5HT2A antagonism by nefazodone may improve motor

symptoms while being equally effective on depressive symptoms as citalopram [275], consistent with the improvement of depression by pimavanserin (34 mg) administered as monotherapy or adjunctive therapy over 8 weeks in a recent single-arm, open-label, phase II study [276]. Interestingly, decreased brainstem (raphe) echogenicity predicted response to SSRIs [202].

Despite evidence that cholinergic deficit is involved in PD depression and dementia, well-conducted clinical trials remain scarce. Although effective on cognition in PD dementia and dementia with Lewy bodies, the effectiveness of donepezil (5–10 mg) was modest on depressive symptoms in an open-label study over 20 weeks [277]. Notably, weekly subcutaneous injection of exanetide (2 mg), an agonist of the GLP-1 receptor abundant in limbic structures, also contributed to improvement of depressive symptoms sustained over 48 weeks, in a recent single-center, randomized, double-blind, placebo-controlled trial that evaluated 62 patients with PD to investigate neuroprotection [278].

4.3 Non-Pharmacological Interventions

STN-DBS is highly effective for the control of motor complications of PD, with a generally favorable effect on depression, impulse control disorders and non-motor fluctuations [279–281], contrasting with possible worsening of apathy following STN-DBS [282], partly mediated by dopaminergic withdrawal and reversed by dopamine agonists [251, 283]. Better non-motor outcome is classically related to a more anterior, medial, and ventral stimulation site, mapping with limbic connections of the STN [284], whereas thalamic and pallidal stimulation are regarded as more neutral for mood. However, postoperative depression is regarded as the main risk factor for suicide after STN-DBS [285]. Some studies have suggested a greater risk of suicide attempt after STN-DBS than in the general population within the first 3 years after surgery [286], but others did not support this finding [287].

The use of repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex in PD depression could provide some, but modest, improvement [21, 288]. Contrastingly, meta-analyses confirmed that electroconvulsive therapy had important beneficial effects for both motor symptoms and severe depression in PD [289, 290].

In addition, randomized clinical trials consistently demonstrated the effectiveness of cognitive behavioral therapy in depressed patients with PD [21, 288]. Interestingly, use of telemedicine with video-to-home cognitive behavioral therapy was recently demonstrated to be an effective treatment in randomized controlled clinical trials in comparison with usual clinic-based treatment [291], in addition to the efficacy of telephone-based cognitive behavioral therapy [292,

293], confirming an earlier randomized controlled trial in depressed PD outpatients [294].

Finally, physical activity in PD [295] and other neurodegenerative disorders [296] may have a beneficial effect to treat depression, in addition to global and motor benefits, in particular for aerobic training exercise, Qiqong, dance, and weekly or biweekly yoga. Indeed, exercise was demonstrated to enhance mesolimbic functioning and increase dopaminergic release in the caudate nucleus [297], and may promote the anti-inflammatory response [298, 299]. Efficacy of expression therapy also suggested that ‘laughter was the best medicine’ [300]. In addition, in a randomized controlled trial, bright-light therapy was found to be effective for depression in PD [301].

5 Conclusions and Future Developments

Enhancement of SSRI efficacy could be evaluated, especially in non-responders. This relates to the use of S-adenosyl methionine in monotherapy [302] or add-on therapy [303]. This component is involved in catechol-O-methyltransferase (COMT)-dependent metabolism of catecholamines and serotonin [304]. Combined therapy using mirtazapine and fluoxetine may also prove effective [305] but remains untested in PD. In addition, no definitive evidence is available regarding the antidepressant efficacy of bupropion in PD [306–308], presenting a favorable dual norepinephrine and dopamine reuptake inhibition profile. Triple reuptake inhibitors may also have a favorable outcome in PD to alleviate both motor and non-motor symptoms [309–311]. Overall, accurate diagnosis of depression, even when its severity is considered mild, and recognition of comorbid motor and non-motor symptoms in PD, at each stage, is critical to offer effective relief for the patient and improve quality of life. Undoubtedly, further research is needed to improve the performance of screening tools in the clinical context, and simplify the use and enhance the specificity of clinical scales for depression, apathy and anxiety in patients with PD [38, 312]. These developments will prove instrumental for the recognition of imaging biomarkers specific to PD depression, which may in turn serve as enrichment biomarkers in clinical trials [313].

However, increasing understanding of pathophysiological mechanisms already help to implement tailored interventions in PD depression and related comorbid symptoms by targeting the neurodegenerative processes that underpin PD subtypes and their prognosis. Furthermore, it is expected that the occurrence and course of PD depression will change with the development of disease-modifying treatments and interventions to promote compensatory plasticity, in particular in patients with prodromal and early PD.

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