Depression in Parkinson disease—epidemiology, mechanisms and management

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Abstract | Depression occurs in around 35% of patients with Parkinson disease (PD) and is often persistent. Symptoms of depression can be evident in individuals at the time of diagnosis and might develop in the premotor stage of the disease. The underlying mechanisms of depression in PD are not known in detail, but changes in brain structure, signaling by neurotransmitters, and levels of inflammatory and neurotrophic factors are all suggested to contribute to its development. Psychosocial factors and pain could also have roles in depression. Changes in dopaminergic, noradrenergic and serotonergic systems in patients with PD might help to explain the incidence of depression in these individuals. Antidepressants that have dual serotonergic and noradrenergic effects are the drugs of choice for treating depression in PD. However, antiparkinsonian drugs might have beneficial effects not only on the motor symptoms of disease, but also on a patient's mood. Deep brain stimulation can worsen depression in some patients, but a preliminary study has suggested that transcranial magnetic stimulation could improve symptoms of depression. This Review describes the frequency and course of depression in patients with PD. The mechanisms that underlie depression in this disease are also discussed, and the management strategies for these patients are highlighted.

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Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder, after Alzheimer disease, and affects more than 1% of the elderly population worldwide.[1] Although PD is predominantly defined as a movement disorder, a wide range of nonmotor symptoms also occur in patients with this disease. Depression is one of the most common of these symptoms, occurring in around 35% of patients. Although depression is a common symptom of other diseases and often occurs in elderly people in general, the evidence suggests that depression is more frequent in patients with PD than in the general elderly population or in patients with other chronic and disabling diseases, such as osteoarthritis.[2] The hypothesis that PD-specific factors might contribute to depression is supported by the fact that some changes in the brain that are known to be involved in the pathogenesis of PD—such as monoaminergic deficits and lesions of frontal–subcortical circuits—could also be associated with depression.[3] Depression is also a key determinant of poor health-related quality of life in patients with PD,[4] and is associated with reduced functioning, cognitive impairment and increased stress for carers of individuals with PD. Understanding depression in patients with PD is, therefore, critical to achieve the optimal care that is needed for patients with this disease.

In this article, we review the relationship between depression and PD, and focus on new evidence regarding the epidemiology of depression in PD. We focus on evidence from studies of depression as a potential risk factor for PD, and from research that investigated whether depression can occur in early stages of the disease, perhaps even before the patient presents with motor impairments. The mechanisms that could underlie depression in PD are discussed, including traditional neurotransmitter-based theories, and novel hypotheses, such as changes in neuroinflammation levels and brain morphology. Finally, we critically review the evidence base for the treatment of depression in patients with PD, including strategies that go beyond the traditional transmitter-based antidepressant therapies.

Epidemiology

Prevalence and incidence of depression

Most studies of depression in different populations report that this mood disorder is more common in patients with PD than in healthy individuals or in those with other diseases.[2] Only a few studies have explored the incidence of depression in patients with PD, and the reported rates vary considerably (Table 1); for example, the two largest studies report the annual incidence of depression in patients with PD to be 2.6% and 13%. Methodological factors, such as differences in

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Key points

- Depression occurs in around 35% of patients with Parkinson disease (PD)
- Mild depression is often persistent in patients with PD, and is a risk factor for moderate to severe depression
- The etiology of depression in PD is not clear, but changes in neurotransmitter (monoaminergic) signaling and limbic Lewy body pathology might contribute
- The roles of other pathologies (such as cerebrovascular disease) and neurotrophic changes in depression are not known
- Pramipexole and nortriptyline are the only agents that have shown antidepressant effects in placebo-controlled clinical trials in patients with PD

patient selection procedures and in the definition and measurement of depression, could have contributed to this variation in frequency.

Core symptoms of depression are depressed mood, loss of pleasure (anhedonia), and feelings of worthlessness or guilt. Somatic symptoms—such as loss of appetite, sleep disturbances, psychomotor retardation, and altered facial expression—are also part of the depression syndrome. However, these symptoms are also evident in patients with PD who are not depressed. Differentiating between depression and PD can, therefore, be difficult, and efforts to do so could result in both overdiagnosis and underdiagnosis of depression in this setting. Attempts have been made to establish clinical criteria for depression in patients with PD on the basis of the mood categories from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).[5] According to these criteria, clinicians should not attempt to decide whether a patient's symptoms arise from depression or PD. Instead, to avoid underdiagnosis, an 'inclusive' approach (in which somatic symptoms should be considered as part of the depression rather than PD) is recommended.[5] A number of clinical and self-report rating scales for mood disorders can provide clinicians with psychometric data that can assist in the diagnosis of depression in a patient with PD.[6]

A systematic review of patients with PD concluded that 17% present with major depression, 22% with minor depression, and 13% with dysthymia,[7] with lower rates of major depression (7.7%) being reported in population-based studies.[8] Clinically relevant depressive symptoms were present in 35% of patients with PD.[7] Several large-scale studies that investigated clinical cohorts were subsequently published, and their findings are consistent with those of the systematic review, suggesting that the prevalence of clinically relevant depression in patients with PD is 30–35%.[9–17] In one large study that included more than 1,400 patients, depression was more common in female than in male patients, and was more prevalent in individuals in the advanced stages of PD and those with dementia than in patients with less-severe disease.[12] Through the use of objective statistical methods, a large study found comorbid anxiety in 50% of depressed patients with PD,[13] a proportion similar to that in the general population with depression. Few studies have explored depression in the early stages of PD, but the available evidence suggests that 10–15% of patients have clinically relevant depressive symptoms at the time of diagnosis (Table 2).

Course of depression

Few investigations have studied the course of depression in PD longitudinally. A study published almost two decades ago reported that 10 of 18 patients with PD (55.6%) who were diagnosed as having major depression still had major depression after 1 year of follow-up, six (33.3%) had minor depression at this time point, and only two patients (11.1%) were in remission from depression.[18] The researchers also identified a positive association between major (but not minor) depression and rapid cognitive decline.

In a study that assessed the level of depression in patients with early PD every 3 months over a 12–18 month period, approximately half of the patients who had

Table 1 | Studies on the incidence of depression in patients with PD

Study	Characteristics of nondepressed patients	Baseline status of PD	Design and follow-up duration	Definition of depression	Risk factors for incident depression	Patients with newly identified depression per year (%)
Dooneief *et al.* (1992)[116]	*n*=129, mean age 71 years (clinic-based cohort)	Prevalent	Retrospective, 5 years	Chart diagnosis	No clinical correlates	1.86
Kulkantrakorn *et al.* (2007)[117]	*n*=59, mean age 69 years (clinic-based cohort)	Prevalent	Prospective, 1 year	ICD 10 after CIS-R	Not significant	5.10
Ravina *et al.* (2009)[16]	*n*=413, mean age 61 years (clinical trial cohort)	Early	Prospective, 1.2 years	GDS-15 ≥5	GDS15*, age, duration of PD	13.80
Becker *et al.* (2011)[118]	*n*=3,637, no data on age (GP Registry)	Incident	Registry study, 10 years	Recorded affective code	Female sex, age, duration of PD	2.60
Starkstein *et al.* (1992)[18]	*n*=92, mean age 66 years (clinic-based cohort)	Prevalent	Prospective, 1 year	DSM-IIIR major and minor	No data	Major: 0.00 Minor: 10.00

*Positive association with persistence of depression. Abbreviations: CIS-R, revised clinical interview schedule; DSM-IIIR, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; GDS-15, 15-item Geriatric Depression Scale; ICD-10, International Classification of Diseases, 10th edition; PD, Parkinson disease.

Table 2 | Studies of depression in patients with Parkinson disease

Study	Patient characteristics (study location)	Measurement scale	Hoehn and Yahr scale score	Duration of disease (years)	MMSE score	Proportion of patients with depression (%)
Martinez-Martin *et al.* (2007)[9]	545 clinic patients without dementia, mean age 67.7 years (international)	NMSQ	2.5 (mean)	7.0	No dementia	50.1
PRIAMO study: Barone *et al.* (2009)[10]	1,072 clinic patients, mean age 67.4 years (Italy)	NMSQ	2.0 (mean)	5.1	11% <23.8	22.5
Negre-Pages *et al.* (2010)[11]	422 clinic patients without dementia, mean age 68.6 years (France)	HAM-D (score >7)	2.2 (mean)	5.4	Mean 28.0 MMSE >23	HAM-D 8–10: 25.0 HAM-D ≥11: 15.0
GEPAD study: Riedel *et al.* (2010)[12]	1,449 clinic patients, mean age 70.7 years (Germany)	MADRS (score ≥14)	1–2: 44.2% 3: 38.7% 4–5: 17.1%	5.8	27.2	23.8
PROMS-PD study: Brown *et al.* (2011)[13]	513 clinic patients, mean age 67.9 years (UK)	GMS, HADS	1–2: 12.6% 3–4: 80.2% 5: 7.2%	6.9	27.9	HADS 8–10: 22.0 HADS >10: 13.0
Kulisevsky *et al.* (2008)[14]	1,351 clinic patients without dementia, mean age 70.6 years (not specified)	NPI	1: 15.1% 2: 42.2% 3: 31% 4–5: 11.8%	5.7	No dementia	Any: 68.9 NPI score >3: 29.9
Vanderheyden *et al.* (2010)[15]	1,086 patients (not specified)	MINI	No data	No data	No data	15.6
Ravina *et al.* (2009)[16]	413 clinical trial patients, mean age 61 years (not specified)	GDS-15 (score ≥5)	1.5 (mean)	0.5	No data	13.8
ParkWest study: Aarsland *et al.* (2009)[17]	175 patients with incident PD, mean age 67.8 years (Norway)	NPI	2.0 (median)	2.0	27.8	Any: 24.3 NPI score >3: 10.3
Kang *et al.* (2005)[115]	162 patients, population-based (not specified)	GDS (score ≥7)	No data	0.0–3.0	No data	13.0

Abbreviations: GDS, Geriatric Depression Scale; GMS, Geriatric Mental State; HADS, Hospital and Anxiety Depression Scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MINI, Mini International Neuropsychiatric Interview; MMSE, Mini-Mental State Examination; NMSQ, Nonmotor Symptoms Questionnaire; NPI, Neuropsychiatric Inventory.

depression at baseline experienced remission of their depressive symptoms by 6 months.[16] However, the risk of developing moderate to severe depressive symptoms was six times higher among patients with mild depression at baseline than in those who did not have depression at baseline. Multivariate analyses indicated that in addition to higher depression scores at baseline, older age and longer duration of PD were associated with a lower likelihood of remission. More long-term studies of depression are needed to identify the course, predictors and prognostic significance of depression in patients with PD.

Depression as a risk factor for PD

The hypothesis that depression precedes PD has been explored in several studies. A strong correlation between a history of depression and an increased risk of subsequent development of PD was identified in eight of nine studies reviewed.[19] Few studies have explored the timing of onset of depression relative to that of PD, but such studies are pivotal to determine whether depression is a prodromal condition of PD (in which case the time lag between onset of depression and onset of PD would be short) or whether it is a risk factor for PD (in which case an extended time lag between onset of depression and onset of PD would be expected).

The question of whether depression is a PD-associated condition or a risk factor for the disease was addressed in a study of 371 patients with incident PD.[20] The results showed that these patients were more likely to have received a diagnosis of depression in the period immediately before being diagnosed with PD than were their disease-free siblings or healthy individuals in the general population. However, a statistically significant effect was only evident in male patients, who were diagnosed with and treated for depression more often than were control men in the general population. This association was seen when the researchers considered the 2–5-year period before diagnosis of PD, but not when they analyzed the period beyond 5 years preceding diagnosis. This finding supports the hypothesis that depression is a prodromal symptom of PD and not a risk factor for disease. In further support of this hypothesis, a registry-based study showed that subsequent development of PD was more common among patients who used antidepressant than among non-users, particularly within the first 2 years after the patients started taking these medications.[21]

Some studies have described a 'parkinsonian' personality type: in a large, population-based study with over four decades of follow-up, individuals with anxious and pessimistic personalities (but not those with depressive traits) had an increased risk of developing PD.[22] Depression might also be a presenting symptom of PD in a small proportion of patients.[23] Marked hyperechogenicity of the substantia nigra and reduced

brainstem raphe echogenicity (suggestive of structural alterations at these sites) is particularly common and severe in patients who have both PD and depression, and these changes in the brain are associated with a history of depression before the development of PD.[24] This observation, coupled with the finding that depression can precede motor symptoms in patients who develop PD, is consistent with the Braak hypothesis of PD,[25] which proposes that pathology in key brainstem nuclei—in particular, the noradrenergic coeruleus–subcoeruleus complex and the serotonergic caudal raphe nucleus —occurs before motor symptoms.

Mechanisms

Depression in people older than 65 years is complex and can be affected by psychosocial issues, genetic factors and changes in the brain, as well as a patient's medical condition. Various changes in the brain might contribute to late-life depression, including monoaminergic disturbances, cerebrovascular disease, Alzheimer disease, Lewy body pathology, functional changes in the limbic and subcortical circuits, hippocampal atrophy, alterations of neurogenesis and neurotrophic factors, and toxic stress, with hypercortisolemia and inflammation.

Genetic factors

An increased risk of depression in first-degree relatives of patients with PD has been reported, which suggests that depression may share familial susceptibility factors with PD.[26] However, few studies have explored the specific genetic factors that could be associated with depression in patients with PD. Some studies have suggested an association between the *SLC6A4* (sodium-dependent serotonin transporter [SERT]) gene and depression, but these studies had small sample sizes and showed inconsistent results.[27–29] A large study published in 2008 found that serotonin (5-hydroxytryptamine, or 5-HT) or dopamine transporter genes did not contribute to depression in patients with PD.[30] Depression does not seem to be associated with any of the genetic forms of PD,[31] although the results of one study suggest that depression is more common in carriers of the Gly2019Ser mutation in *LRRK2* (leucine-rich repeat kinase 2) than in noncarriers.[32]

Neuroanatomy of depression

A unifying model of neurodegeneration in depression and PD was proposed in 1995.[33] This model suggests that primary degeneration of dopaminergic mesocortical and mesolimbic neurons leads to dysfunction of the orbitofrontal cortex, which secondarily affects serotonergic cell bodies in the dorsal raphe nuclei. Additional circuits that are proposed to be affected in patients with depression include the basotemporal limbic circuit, which links the orbitofrontal cortex to the anterior temporal cortex through the uncinate fasciculus, and the orbitofrontal cortex–basal ganglia–thalamic circuit. This model has received partial support from subsequent studies showing that patients with PD and depression had a profound loss of striatal dopamine transporter availability[34] and frontal hypoperfusion compared with nondepressed PD patients.[35] Hypometabolism of glucose in the head of the caudate nucleus and in the inferior orbital region of the frontal lobe was identified in depressed individuals with PD, relative to glucose metabolism in the same area in nondepressed patients with PD and healthy controls.[36]

Depression-associated structural and functional changes in the brain can be identified using imaging techniques, such as structural and functional MRI, as well as ^{18}F-fluorodeoxyglucose PET. As changes in limbic areas of the frontal cortex and striatum occur in depression, some studies have focused on imaging of frontostriatal circuits.[36] Few structural imaging studies have investigated changes in the brains of patients with PD; however, the results from a diffusion tensor imaging study[37] and a volumetric MRI study[38] suggested that loss of white matter within the cortical–limbic network was positively associated with depression.

Deep brain stimulation

On the basis of neuroanatomical and electrophysiological studies in rodents, nonhuman primates and humans, deep brain stimulation (DBS) has been developed for the treatment of patients with PD. DBS of the subthalamic nucleus is reported to improve motor symptoms and quality of life in patients with advanced PD,[39] but individuals who receive the treatment seem to have an increased risk of suicide. A large, international, multicenter, retrospective survey of patients who underwent DBS of the subthalamic nucleus found high rates of completed (0.45%) and attempted (0.90%) suicide in treated individuals.[40] In addition, the suicide rate of patients in the year following the operation (0.26%) was much higher than the rate expected from WHO data (0.02%).[40] In contrast to subthalamic stimulation, which can worsen depression, pallidal stimulation improves depression in patients with PD. Pallidal stimulation is, therefore, more frequently used than subthalamic stimulation for the treatment of patients with PD who have comorbid psychiatric symptoms.[41]

DBS can be targeted to neuroanatomically defined locations, and the procedure is reversible (that is, the stimulation can be stopped). These properties mean that DBS can assist in identifying the potential pathophysiological role of distinct neuronal circuits that are involved in depression in patients with PD and, thus, the neuronal circuits that could be targeted by antidepressant therapies. Indeed, various case reports describe patients with PD who experienced transient, acute (but reversible) major depression when DBS was targeted to the substantia nigra.[42,43] These data suggest that the nigrostriatal pathway has an important role in the pathophysiology of depression in this setting. Specific DBS protocols have not yet been defined for use in the treatment of depression in patients with PD. However, several studies have demonstrated that DBS of the subgenual cingulate cortex[44] and the nucleus accumbens[45] can successfully alleviate depressive symptoms in

non-PD patients with major depression that is refractory to medical treatments. Future studies should aim to develop DBS procedures that target both motor and nonmotor symptoms of PD.

Neurotransmitter systems

Most of the studies that have explored the mechanisms underlying depression in patients with PD have focused on neurotransmitter systems, such as the noradrenaline, dopamine and 5-HT systems, which are known to be affected in PD. These neurotransmitter systems are also involved in regulation of mood, and alterations in these systems are associated with depression in the general population and in patients with neurodegenerative diseases other than PD.

5-hydroxytryptamine

In an autopsy study, patients who had PD and depression at the time of death had increased serotonergic neuronal cell loss in the dorsal raphe nucleus compared with nondepressed patients with PD.[46] Studies that used transcranial sonography have shown that reduced echogenicity in the mesencephalic raphe (which represents loss of serotonergic neurons at this site) is associated with depression in patients with PD.[47] Reduced levels of the serotonergic metabolite 5-hydroxyindoleacetic acid have been found in the cerebrospinal fluid (CSF) of depressed patients with PD, in comparison with nondepressed patients with this disease.[48,49] However, subsequent studies found no association between the levels of any biogenic amine in the CSF and the severity of depression in patients with PD,[50] and also indicated that the mood of nondepressed patients with PD was not affected by acute tryptophan depletion.[51] The findings of these two studies suggest that reduced 5-HT activity does not affect vulnerability to depression in patients with PD.

Studies on postmortem brain tissue samples from patients with PD found that striatal levels of both 5-HT and its transporter SERT were decreased by 30% and 66%, respectively, in patients with PD compared with healthy controls. The reduced availability of these molecules was more apparent in the caudate nucleus than in the putamen.[52] Autopsy studies of patients who had dementia with Lewy bodies found that 5-HT_{1A} receptor density was significantly higher in the temporal cortex of patients with depression than in those without depression.[53] This increased receptor density could result from secondary upregulation of the receptors, owing to reduced serotonergic activity in depressed patients. Indeed, preservation of SERT reuptake sites in the parietal neocortex has been reported in patients with depression, compared with unaffected individuals.[54] These findings challenge the assumption that downregulation of serotonergic markers and reduced cortical monoamine functioning are responsible for depression in patients with Lewy body dementia.

Functional PET studies have also shown that SERT availability is decreased by around 30% in the striatum of patients with PD,[55] and that this receptor is also downregulated in various other brain regions, including the orbitofrontal cortex, cingulate cortex, insula, amygdala and hippocampus, of patients with PD.[56,57] Some studies showed that 5-HT availability was higher in the raphe nuclei and limbic regions of patients with PD who had depression, compared with nondepressed patients with this disease,[58,59] although this finding was not evident in all studies.[60] Reduced binding of 5-HT to the $5HT_{1A}$ receptor in the midbrain raphe was observed in patients with PD, but receptor binding did not differ between depressed and nondepressed patients.[61]

In one study, loudness-dependent auditory evoked potentials were used as a readout of serotonergic function.[62] This parameter was reduced in drug-naive patients with PD, although reduced serotonergic function was not associated with depression.[62] In patients with advanced PD, the conversion of levodopa to dopamine might be carried out by serotonergic projections that innervate the striatum,[63] which could lead to displacement of 5-HT owing to the presence of this 'false dopamine' in serotonergic nerve terminals. This displacement could result in lowered levels of 5-HT, which could in turn affect 5-HT metabolism. In fact, chronic treatment with citalopram—a selective serotonin reuptake inhibitor (SSRI)—in patients with PD and concurrent major depression did not cause the decrease in 5-HT that was seen in patients with depression alone.[64] These findings suggest that patients with PD have impaired autoinhibition of 5-HT metabolism.

Dopamine and noradrenaline

The marked reduction in activity of nigrostriatal dopamine and other dopaminergic pathways (such as those serving limbic and frontal circuits) in patients with PD, coupled with the association between dopamine and regulation of mood and reward systems, makes a reduction in dopamine levels an attractive hypothesis for the mechanism underlying depression in these patients. Indeed, loss of dopaminergic neurons in the ventral tegmental area is suggested to be associated with depression in patients with PD.[65]

Similarly, noradrenaline is thought to be associated with symptoms of idiopathic depression.[66] The locus coeruleus is the major noradrenergic structure in the brain, from which widespread noradrenergic neurons project to limbic areas and other regions of the brain. The locus coeruleus is affected by neurodegeneration in the early stages of PD, and increased degeneration within this region has been reported in depressed individuals with PD compared with nondepressed patients with this disease.[67] Moreover, one study in patients with PD reported that reduced binding of the PET radionuclide ^{11}C-RTI-32 (tolpane) in the limbic and ventral striatum (which is suggestive of reduced levels of dopamine and noradrenaline transporters in these regions) was associated with depression.[68] In another study, patients with advanced PD, both with and without depression, had reduced levels of the noradrenaline metabolite 3-methoxy-4-hydrophenylglycol in their CSF compared with patients with depression alone.[64]

Acetylcholine

The association of cognitive impairment with both depression and cholinergic deficits in patients with PD suggests that cholinergic deficits could underlie depression in these individuals. Indeed, cortical cholinergic denervation was found to be associated with depression in patients with PD, independent of their cognitive functioning.[69] Further evidence for an association between cholinergic transmission and depression in PD was provided by a study showing that reduced availability of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor was associated with mild depressive symptoms.[70]

Summary

Findings from a variety of sources, including functional imaging studies, CSF analysis and studies of brain tissue obtained at autopsy, suggest that dysfunction of basal ganglia dopaminergic circuits that project into the dopaminergic frontal lobe, as well as of noradrenergic limbic and brainstem structures, is associated with depression in patients with PD. The findings regarding a link between 5-HT and depression in patients with PD are inconsistent. However, most of the available studies were performed in patients with mild depression, and the role of 5-HT might differ in patients who have major depression.

Inflammation, stress and trophic factors

Emerging evidence suggests that stress hormones, immunomodulatory mediators, neurotrophic factors and neuropeptides are involved in the pathophysiology of depression,[71] and possibly in PD as well (Figure 1). In one study, in which researchers investigated the levels of IL-1β, IL-6, IL-10, tumor necrosis factor (TNF) and cortisol in patients with PD and depression, high levels of TNF—a cytokine that has neuromodulatory effects in the brain—were associated not only with depression, but also with impaired cognition, sleep and disability.[72] In another study, patients with PD and major depression had lower levels of both cortisol and IL-6 in their CSF than patients who only had depression.[64] The reduction in levels of IL-6 persisted in the depressed patients, even after treatment with citalopram. CSF levels of IL-6 and cortisol could, therefore, distinguish between patients with PD and concomitant major depression and patients with depression alone.

Prolonged stress-induced activation of the brain via glucocorticoids and their receptor has a negative effect on cellular plasticity, resilience and neurogenesis, processes that are all cellular mediators of depression. Indeed, major depression is associated with hyperactivation and reduced feedback inhibition of the hypothalamus–pituitary–adrenal (HPA) axis.[73] Evidence exists that hyperactivation of the HPA-axis also occurs in patients with PD, but the role of the HPA axis in depression specifically in patients with PD remains to be clarified.[74]

Brain-derived neurotrophic factor (BDNF) is involved in the pathophysiology of both PD and depression. BDNF levels are decreased in the substantia nigra of patients with PD, as well as in the hippocampus and serum of depressed individuals; treatment with antidepressant drugs or electroconvulsive stimulation increases the production of BDNF in the hippocampus and cortex.[75] Few studies have investigated the role of BDNF in patients with depression and PD, but one study reported that depressed patients with PD had lower plasma BDNF levels than either nondepressed patients or healthy control individuals.[76] The plasma BDNF levels in depressed patients were normalized by treatment with antidepressant drugs.

The effects of BDNF are mainly exerted via BDNF and NT-3 growth factor receptors and activation of multiple signaling pathways, including the mitogen-activated protein kinase (MAPK)–MEK and Akt–glycogen synthase kinase-3 (GSK-3) pathways, which induce the transcription of the gene encoding p11—a protein that is involved in transporting molecules, including 5-HT receptors, to the cell surface (Figure 1).[77] Each of the molecules downstream of BDNF activation has been implicated in both depression and PD, and transcription of the p11 gene is reduced both in patients with depression and in animals after induction of PD-like symptoms.[78] Downregulation of the MAPK–MEK pathway by a negative regulator of this signaling cascade causes depression-like symptoms in animals, and the symptoms can be reversed by treatment with antidepressant drugs[79] or by stimulation of dopamine receptors.[80] Lithium, which is commonly used to treat patients with bipolar disorder or refractory depression, is an inhibitor of GSK-3, and is also implicated in the neurodegenerative process underlying PD.[81]

Neurogenesis is impaired in PD[82] and is also suggested to be associated with depression.[83] This hypothesis is based on the observation that prolonged stress and inflammation, via activation of transcription factors like the glucocorticoid receptors and nuclear factor κB, decrease adult neurogenesis in the hippocampus, and the fact that newly generated neurons in the dentate gyrus are required for mediating some of the beneficial effects of antidepressant treatment.[83] Whether neurogenesis is functionally involved in depression in patients with PD is unknown and remains to be explored.

Although the evidence is still limited, the findings of the studies described above, when taken together, suggest that immunomodulatory and neurotrophic factors are associated with depression in patients with PD, and that they could be affected by antidepressant treatments.

Lewy body pathology

Little is known regarding the pathological underpinnings of late-life depression in either the general population or in patients with PD. In a population-based, prospective study of the neuropathological correlates of late-life depression, Lewy body pathology (but neither vascular nor Alzheimer disease pathologies) in the substantia nigra and locus coeruleus was found in 153 patients without dementia who had depression during the observation period.[84] Neuronal loss in the hippocampus, as well as in the nucleus basalis, raphe nucleus and locus coeruleus, was also associated with depression. The number of patients with Lewy body pathology was

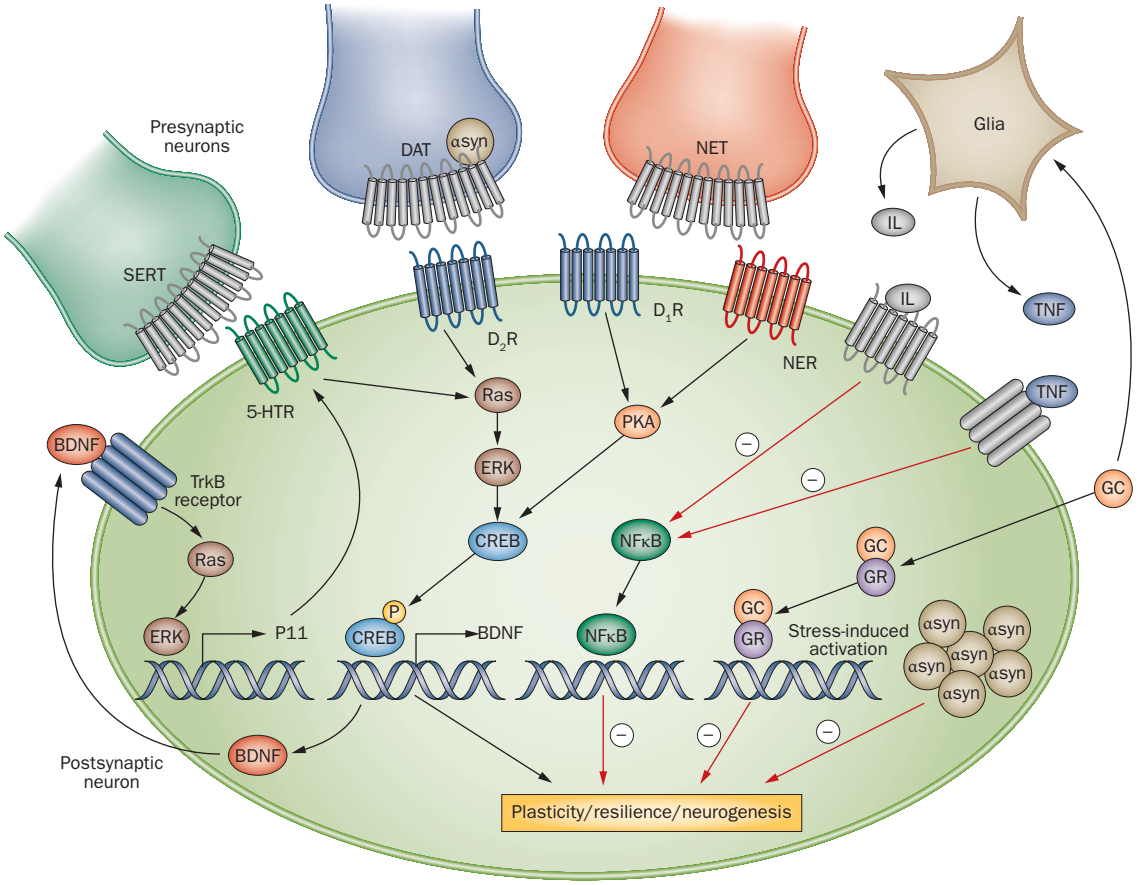

Figure 1 | Neuronal factors and signaling pathways implicated in depression in PD. Downregulation of monoamines, particularly dopamine and noradrenaline, might underlie depression in patients with PD. Stimulation of monoamine receptors activates several signaling cascades, which eventually leads to increased levels of BDNF. This mediator supports cellular plasticity, resilience and neurogenesis, and drives the expression of the monoamine receptor adaptor protein p11 (which, in turn, increases the efficacy of some 5-HT receptors at the neuronal surface). Large amounts of glucocorticoids and inflammatory markers (such as TNF and interleukins) are released from glial cells and act via transcription factors, such as the glucocorticoid receptor and NFκB, to exert a negative influence on neuronal plasticity, resilience and neurogenesis. Increased α-synuclein load could increase the risk of depression by negatively affecting dopamine transmission, neuronal plasticity and regeneration. Abbreviations: 5-HT, 5-hydroxytryptamine; 5-HTR, 5-HT receptor; αsyn, α-synuclein; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP response element binding protein; DAT, dopamine active transporter; D_1R, dopamine receptor D_1; D_2R, dopamine receptor D_2; ERK, extracellular signal-related kinase; GC, glucocorticoid; GR, glucocorticoid receptor; IL, interleukin; NER, norepinephrine receptor; NET, norepinephrine transporter; NFκB, nuclear factor κB; PD, Parkinson disease; PKA, protein kinase A; SERT, sodium-dependent serotonin transporter; TNF, tumor necrosis factor; TrkB, BDNF/NT-3 receptor.

small, but all three patients who had moderate or severe nigral involvement and all three patients who had locus coeruleus Lewy body pathology also had depression. Further evidence in support of the role of Lewy body pathology in depression emerged from the study of a patient with Lewy bodies in the hippocampal region, cerebral cortex and brainstem nuclei, who presented with late-life major depression but had no other symptoms typically associated with Lewy body disease.[85]

Cerebrovascular disease

Cerebrovascular disease is increasingly common in older people and good evidence links this condition with depression in late life.[86] Cerebrovascular disease can induce parkinsonism, which is often called vascular parkinsonism, but some evidence from imaging and pathological studies also suggests that the effect of cerebrovascular disease on clinical symptoms in patients with idiopathic PD is more pronounced than its effect in elderly people without PD.[87] Mechanisms that could contribute to the increased burden of cerebrovascular disease in patients with PD include orthostatic hypotension with reactive supine hypertension, immobility, cardiac valvopathy, and elevated homocysteine levels due to levodopa treatment. Cerebrovascular disease is associated with gait and balance disturbances and cognitive impairment in patients with PD, but its association with depression in PD has not yet been studied.

Pain

Two-thirds of patients with PD report feelings of pain, including musculoskeletal pain and neurogenic or psychogenic pain syndromes.[88] Chronic pain contributes

to depression in people in general,[89] and could also contribute to increased depression in patients with PD. Indeed, a strong association has been identified between pain and depression in patients with PD.[90] This finding might also have implications for the management of these patients, since it is possible that treatment of pain might also alleviate depression in people with PD, and treatment of depression might reduce pain. Studies exploring these hypotheses are needed.

Psychosocial aspects

That the complex syndrome of depression is caused only by the neurodegenerative brain changes that occur in patients with PD is a naive assumption. The evidence indicates that psychosocial factors can also contribute to the depressive state in these patients.[91] Receiving a diagnosis of a chronic disabling disease is in itself a stressful life event, and the coping strategy of each individual will vary, depending on their pre-existing psychological status. A patient's personality, social situation, support, and learned defense mechanisms could also affect how they cope with receiving the diagnosis of PD. Research into such factors is challenging, and the evidence for the effect of these factors on depression in physically disabled individuals is limited.[92]

Of note, biological factors together with clinical and demographic factors account for only a small proportion of the variables that could be linked to depression in patients with PD. Disability is the most common reason underlying depression in these patients, and explained 16% of cases of depression in one study.[93] However, the researchers found that if broad psychological and social factors such as self-esteem, coping style, and practical support were included in the self-reported assessment, the underlying cause of depression could be identified in 44% of patients with PD. In some studies, depression was common in both the initial and the more-advanced stages of PD; the mechanisms underlying this mood disorder might differ between the early and late stages of disease. Factors such as young age at onset of PD and rapid progression of the disease were associated with depression in some studies. These findings suggest that the psychosocial consequences of developing PD at an early age, the associated important familial and occupational consequences, and the challenge of adapting to rapid progression of symptoms and disability, might contribute to the development of depression.[94]

Management

Antidepressant therapies

SSRIs are the most commonly used antidepressants in patients with PD; however, controlled clinical trials, systematic reviews and meta-analyses suggest that these agents are no more effective than placebo in treating depression in this setting (Table 3).[95–96] A similar lack of efficacy of SSRIs is emerging in other neurodegenerative diseases, such as Alzheimer disease.[97]

An early study, published in 1980, investigated the effects of nortriptyline (a tricyclic antidepressant drug with both serotonergic and noradrenergic activities) and showed a statistically significant reduction of depression compared with placebo in patients with PD.[98] This finding was supported in a subsequent study that included 55 patients with PD who had a depressive disorder, as determined by the DSM-IV criteria. Patients treated with nortriptyline (mean dose of 48.5 mg per day), but not the SSRI paroxetine, had a statistically significant reduction in depression compared with patients who received placebo, with a large effect size of 1.2 and a number needed to treat of 3.5. Treatment with nortriptyline is often associated with adverse effects, such as sedation, hypotension and even worsening of cognition, but the patients in this study who received nortriptyline did not report more of these adverse events than did the placebo group.[99] Patients who showed an improvement in depression scores also had additional benefit in terms of improved quality of life and social functioning. Improvement in depression was maintained in patients who were treated with nortriptyline over a 16-week extension to this study;[100] patients who received the active drug had a lower risk of relapse during the extension phase than those on placebo. However, cognition did not improve in the patients treated with nortriptyline.[101]

Another study, which compared desipramine (a predominantly noradrenergic reuptake inhibitor tricyclic antidepressant) with the SSRI citalopram, showed that an antidepressant effect of desipramine, but not citalopram, was evident after 14 days of treatment, whereas both drugs were superior to placebo in treating depression in patients with PD at the study end point (30 days).[102]

Atomoxetine—a selective noradrenaline reuptake inhibitor—showed no antidepressant efficacy versus placebo in a small study of patients with PD;[103] however, when the definition of efficacy was more liberally applied (a >40% decrease in depression score instead of a >50% decrease), a higher proportion of patients had improved depression when treated with atomoxetine (31.8%) compared with placebo (9.5%). Of interest, global cognition and daytime sleepiness were also improved after treatment with atomoxetine, and the drug was well-tolerated.

The antidepressive effect of venlafaxine— a serotonin–noradrenaline uptake inhibitor—was compared with that of paroxetine and placebo for 12 weeks in 115 patients with PD and depression. According to the results of the study, which have so far only been published in an abstract, both drugs were well-tolerated and were more effective in reducing depression than placebo.[104]

Although these preliminary results are interesting, firm conclusions cannot be drawn from these data before the full report is available. Nonetheless, the emerging evidence suggests that dual-acting antidepressant drugs (those that act on both serotonergic and noradrenergic systems) might be useful in the treatment of depression in PD. Bupropion is another dual-acting antidepressant that inhibits both dopamine and noradrenaline reuptake, and might be useful for the treatment of depression in patients with PD.[105] Although the few encouraging reports discussed above suggest that novel antidepressant

Table 3 | Placebo-controlled studies of antidepressant drugs in patients with Parkinson disease

Study	Agent(s)	Duration (weeks)	Inclusion criteria	Primary outcome	Number of patients	Effects on reducing depression
Andersen *et al.* (1980)[98]	Nortriptyline	8×2 (crossover study)	Moderate depression	Self-made 31-item scale	22	Greater improvement in nortriptyline period vs placebo period
Allain *et al.* (1991)[119]	Selegiline	12	*De novo* Parkinson disease	HAM-D	93	Selegiline more effective than placebo
Wermuth *et al.* (1998)[120]	Citalopram	52	Major depression (DSM-IIIR)	HAM-D (melancholia scale)	37	Citalopram equal to placebo
Leentjens *et al.* (2003)[121]	Sertraline	10	Major depression (DSM-IV)	50% reduction of pretreatment MADRS	14	Sertraline equal to placebo
Devos *et al.* (2008)[102]	Desipramine and citalopram	4	Major depression	MADRS	48	Day 14: desipramine more effective than placebo; day 30: desipramin and citalopram more effective than placebo
Menza *et al.* (2009)[99]	Nortriptyline and paroxetine	8	DSM-IV major depression or dysthymia, SCID	17-item HAM-D change (% of patients with 50% reduction)	52	Nortriptyline more effective than placebo; paroxetine equal to placebo
Barone *et al.* (2010)[106]	Pramipexole	12	GDS-15 score ≥5 and UPDRS-I, item 3 score ≥2	BDI change	296	Pramipexole more effective than placebo
Weintraub *et al.* (2010)[103]	Atomoxetine	8	IDS-C score ≥22	IDS-C, CGI-I	55	Atomoxetine equal to placebo
Richards *et al.* (2010)[104]	Venlafaxine and paroxetine	12	DSM-IV depression syndrome, or 'subsyndromal depression' (HAM-D score >12)	HAM-D change	115	Venlafaxine and paroxetine more effective than placebo

Abbreviations: BDI, Beck Depression Inventory; CGI-I, Clinical Global Impression (Improvement); DSM-IV, Diagnostic and Statistical Manual of Mental Disorders 4th edition; DSM-III R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; GDS-15, 15-item Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; IDS-C, Inventory for Depressive Symptomatology, Clinician-Rated; MADRS, Montgomery–Åsberg Depression Rating Scale; SCID, Structured Clinical Interview for the DSM-IV; UPDRS-I, Unified Parkinson's Disease Rating Scale, mental subscale.

drugs with dual effect might be beneficial in this setting, no placebo-controlled studies have yet been published in full. Further research into the effect of combined noradrenergic and serotonergic agents on depression in patients with PD is, therefore, warranted.

Antiparkinsonian drugs

The potential involvement of dopamine in the pathogenesis of depression in patients with PD suggests that dopaminergic treatment might improve depression in these individuals. Whereas convincing evidence for the efficacy of levodopa in the treatment of depression is lacking, promising reports from early studies suggested that dopamine agonists are effective in the treatment of depression in patients with PD. These findings have now been substantiated in a large, placebo-controlled clinical trial.[106] Pramipexole (given at a mean dose of 2.18 mg per day) led to a statistically significant reduction in depression scores compared with placebo. The actual improvement in depression was quite small (possibly related to the generally mild depression severity in patients included in the trial), but seemed to be independent of motor improvement.[106] Pramipexole was well-tolerated, and the added benefit of this drug in terms of improving motor function makes it a tempting choice as a first-line antidepressant in patients with PD and depression.

Other dopamine agonists, such as ropinirole, might also have antidepressant properties; however, only one open-label, noncontrolled trial has provided evidence to support the efficacy of this drug in the treatment of depression.[107] Finally, in a randomized, double-blind, placebo-controlled study, the monoamine oxidase B inhibitor selegiline exerted a delayed antidepressant action in patients with PD who were not clinically depressed.[108]

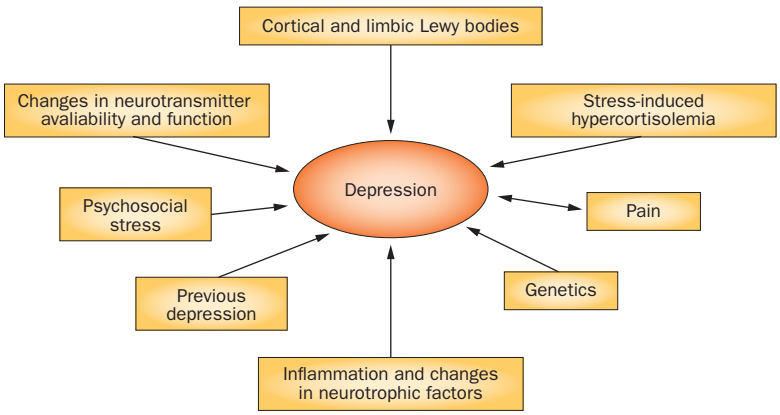

Figure 2 | Factors that might influence depression in patients with Parkinson disease.

Electrical or magnetic stimulation

Electroconvulsive therapy (ECT) is the most effective treatment for idiopathic major depression, and its beneficial effects are thought to be mediated by stimulation of dopamine, noradrenaline and 5-HT systems. A positive

Box 1 | Managing depression in patients with PD

- Diagnose and rate depression and comorbid symptoms (such as anxiety and apathy)
- Remove or treat potential external causes of depression (such as physical disease, environmental stress, substance use or depression-inducing drugs)
- Administer (or increase the dose of) dopamine agonist treatment
- Provide psychological support and guidance
- Antidepressant therapy (nortriptyline 50–100 mg per day, venlafaxine 150 mg per day)
- If depression is severe and the patient does not respond to treatment, electroconvulsive therapy or repetitive transcranial magnetic stimulation should be considered

Abbreviation: PD, Parkinson disease.

effect of ECT on motor symptoms was observed in a controlled study of patients with PD. A number of noncontrolled studies have reported beneficial effects of ECT on depression in patients with PD, but systematic evidence for a positive effect of such treatment on depression is lacking. The main adverse effect of ECT is memory impairment (which is usually transient) and occasional delirium—an outcome that might be more common in patients with PD than in depressed patients who do not have a neurological disorder.[109] Adverse events are less common during unilateral ECT than during bilateral stimulation. ECT should be considered in patients who do not respond to other treatments for depression, but because of the risk of adverse events associated with ECT this procedure should only be considered in patients with moderate to severe depression.

Repetitive transcranial magnetic stimulation (rTMS), a noninvasive method to induce depolarization or hyperpolarization in the neurons of the cerebral cortex, has some antidepressive effects in patients with idiopathic depression who do not respond to other treatments.[110] Preliminary studies have also reported promising results in patients with PD and depression. Patients with PD and mild to moderate depression who received active rTMS had improved depression scores compared with patients who received sham rTMS (placement of the electrodes on the skull, but without magnetic stimulation).[111] These positive effects were evident immediately after stimulation and at 30 days after the end of the 10-day treatment period. Beneficial effects on cognition and motor symptoms were also noted after rTMS therapy, which was well-tolerated.[111] Whether the antidepressive effect of rTMS can be sustained beyond 30 days after the cessation of active treatment is not known.

Psychosocial treatment and psychotherapy

A few noncontrolled studies have suggested that cognitive behavioral therapy can improve depression in patients with PD.[112,113] Studies that used cognitive behavioral therapy and other psychosocial therapies, such as interpersonal psychotherapy, have demonstrated the efficacy of psychotherapy in late-life depression;[114] however, no systematic evidence in patients with PD is yet available. Further studies are, therefore, a priority.

Conclusions

Depression is a common syndrome in individuals with PD, affecting 30–40% of such patients.[7] Evidence from the few longitudinal studies that have been performed suggests that depression is often persistent in patients with PD and can worsen over time.[16,18] Convincing evidence indicates that the occurrence of depression early in life is associated with an increased risk of PD.[19] Depression occurs early in the course of PD in around 10–15% of patients,[16] and emerging evidence shows that depression can be the presenting symptom of PD.[23] Although the exact etiology is still unknown, numerous pathways have been proposed to contribute to depression in patients with PD (Figure 2). Deficits in monoaminergic systems, in particular dopamine deficiency in the frontal and subcortical regions and changes in the noradrenaline pathways, might contribute to this mood disorder.[33,68] Lewy body pathology in the subcortex might itself contribute to the observed high frequency of depression in patients with PD,[84] and emerging evidence also suggests that changes in the levels of inflammatory and neurotrophic molecules could also have a role.[64,72,76]

General strategies for managing patients with PD and depression have been developed (Box 1). Emerging evidence suggests that dopaminergic agonists might provide some benefit in patients with PD and mild depression,[106] and that antidepressants acting on both 5-HT and noradrenaline systems can reduce depression.[99] In addition to adequately powered studies to investigate the effects of antidepressant drugs in patients with PD, future studies should explore the benefits of other management strategies—including psychosocial therapies, drugs that modulate inflammatory and neurotrophic factors, and brain-stimulation strategies (such as ECT, TMS and DBS)—for patients with PD and depression.

Review criteria

A comprehensive review of the literature was conducted by searching MEDLINE and PubMed databases using the following search terms: “Parkinson”, “depression”, “antidepressants”, “electroconvulsive therapy”, “transcranial magnetic stimulation”, “selective serotonin reuptake inhibitors”, “sertraline”, “venlafaxine”, “nortriptyline”, “cognitive behavioral therapy”, and “psychosocial therapy”, alone and in combination. Papers were selected in the basis of title, abstract or full version. Relevant papers were read in full, and we searched the reference lists of identified papers for further leads. Proceedings from the 14th International Congress of Parkinson’s disease and Movement Disorders, Buenos Aires, Argentina (2010) and the 2nd World Parkinson Congress, Glasgow, Scotland, UK (2010) were also searched.

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