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Depression and Parkinson's Disease: Current Knowledge

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Abstract

Depressive disturbances are common in patients with Parkinson's disease (PD) and influence many other clinical aspects of the disease. In addition to causing inherent emotional distress, depressive disorders negatively impact quality of life, motor and cognitive deficits, functional disability, and other psychiatric comorbidities in patients with PD. Knowledge of the pathophysiology of PD depression remains limited. However, clinical studies demonstrate the efficacy of medications and psychotherapies for PD depression, underscoring the importance of their timely detection and concerted management.

Keywords

Depression; Parkinson's disease; Mood disorder; Psychiatric; Antidepressant; Cognitive behavioral therapy; Electroconvulsive therapy; Quality of life; Treatment; Suicide; Major depression: dysthymia; Minor depression; Subsyndromal depression; Epidemiology; Pathophysiology

Introduction

The diagnosis of Parkinson's disease (PD) depends on evidence for a movement disorder characterized by tremor, rigidity, and bradykinesia; however, clinical management requires attention beyond its motor features and needs to involve nonmotor features as well. This is because many patients, over the course of their PD, experience neuropsychiatric disturbances, including depression, anxiety, sleep disturbances, psychosis, and behavioral and cognitive changes [1]. For patients and families, these neuropsychiatric disturbances are often more problematic and distressing than the motor aspects of PD [2].

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Compliance with Ethics Guidelines

Conflict of Interest Laura Marsh has been a consultant for Roche Pharmaceuticals for the development of clinical trial designs to test interventions for apathy in Parkinson's disease. She is employed by the Michael E. DeBakey Veterans Affairs Medical Center. She is a site investigator for the Dystonia Coalition U54 NS065701.

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It is important to emphasize to patients, their families, and other colleagues that depressive disorders in PD are treatable and recovery is possible. Untreated the impact of depression extends far beyond mood symptoms: earlier initiation of dopaminergic therapy, greater functional disability, faster physical and cognitive deterioration, increased mortality, poorer quality of life, and increased caregiver distress [3–6]. Unfortunately, in clinical settings, depressive disturbances are underrecognized and, even when identified, frequently undertreated [6–10]. To close that gap, this review focuses on current knowledge of the epidemiology, pathophysiology, clinical features, and treatment of depressive disturbances in PD. Advances in each of these areas have contributed to a more comprehensive approach to PD with better clinical outcomes.

Epidemiology

It is generally accepted that clinically significant depressive disturbances occur in 40–50 % of patients with PD [11]. As such, depression is one of the most frequently reported neuropsychiatric disturbances in PD. However, the reported prevalence differs according to the definitions of “case-ness,” the population sampled, which depressive subtypes or discrete mood disorders were investigated, and heterogeneity in the presentation and course. Clinical interviews using standardized diagnostic criteria are the “gold standard” for establishing psychiatric diagnoses in research studies. Case-ness can also be defined according to select cutoff scores on self-report or clinician-rated psychiatric symptom rating scales. That approach provides a barometer of prevalence, but underestimates rates since illness severity ranges from mild to marked, symptoms may be episodic or persist, and symptom profiles vary, especially when the symptoms are treated [11].

In cross-sectional studies of PD, slightly less than half of those with depressive disturbances have major depression; most have milder “nonmajor” forms of depression. In one review of PD depression studies, the average prevalence of dysthymia, minor depression, and major depression was 22.5 %, 36.6 %, and 24.8 %, respectively [12]. A more recent systematic review noted lower rates for major depression in population-based studies versus clinical or tertiary-care PD samples [11]. Subsyndromal depression, defined as clinically relevant depressive phenomena that do not meet standardized diagnostic criteria for major or nonmajor depressive disorders, is also evident. For example, patients who experience depressive symptoms only during “off” states may be classified as having subsyndromal depression.

Although not a substitute for a diagnostic clinical interview, depression rating scales are also used to identify clinically significant depressive symptoms, as screening tools to predict the presence of major and minor depressive disorders [13•], or to monitor treatment response. In studies that address motor deficits as a primary outcome, depression scales provide a basis for investigating the secondary effects of the intervention on mood, as well as how depressive symptoms influence motor and other outcomes. For example, an international study of more than 1,000 patients with PD found that over 50 % of the participants reported clinically significant depressive symptoms based on Beck Depression Inventory scores [14]. In most PD samples, depressive symptom severity is mild to moderate. However, substantial numbers of PD patients have moderate-to-severe depressive symptoms [9, 15]. Depressive

symptoms are also more likely to accompany anxiety disorders, cognitive impairment, and psychosis [15].

The few studies examining the incidence of PD depression indicate that depressive disorders can develop at any phase in the course of PD [14]. Frequently, affective disorders predate the onset of motor symptoms—on average, 4–6 years before the diagnosis of PD [16]. Once PD is diagnosed, the annual rates of newly diagnosed depressive disorders range from 1.86 to 10 % (for major depression) [17•] and, subsequently, may have a long-term or a recurrent course [3, 6, 18].

Several longitudinal analyses suggest that depression and its treatment influence the course of motor symptoms. In a placebo-controlled antidepressant treatment trial in PD patients with major depression or dysthymia, improved depression, regardless of the treatment arm, was associated with reduced physical disability and improved quality of life [19]. Similarly, in a prospective clinical trial of potential neuroprotective agents involving 413 patients with recently diagnosed, but untreated, PD, 27.6 % of subjects screened positive over a 15-month follow-up period for clinically significant depressive symptoms (defined as a score of 5 or higher on the 15-item Geriatric Depression Scale) [6]. Whereas depressive symptoms resolved by 6 months in nearly half of the subjects with clinically significant mild symptoms at the baseline, mild depressive symptoms at the baseline were also associated with a sixfold higher rate of developing moderate to severe depressive symptoms during the follow-up period [20]. Depressive symptoms, more so than motor deficits, were the strongest predictor of initiation of dopaminergic therapy [6]. An extension of these longitudinal analyses included five additional clinical trials involving a total of 1,024 subjects with early, unmedicated PD [21]. In this larger sample, treated or untreated mild depression was again associated with greater disability and earlier initiation of dopaminergic therapy. After depression severity had been controlled for, tricyclic antidepressant use, but not selective serotonin reuptake inhibitor (SSRI) use, was associated with a delayed need to initiate dopaminergic therapy [21].

The clinical presentation of depressive disorders in PD is further complicated by higher rates of cognitive dysfunction, somatic complaints, and psychiatric comorbidities [22, 23•]. As in the general population, these features may predict nonresponse to treatment and higher rates of disability, relapse, and recurrence [24, 25].

Pathophysiology

The underlying mechanisms of depression in PD remain unknown. Psychological factors are relevant, but psychosocial factors and disability are not the predominant determinants of depressive disorders in PD [26, 27]. Rather, neurobiological factors associated with the underlying neurodegenerative disease and its somatic treatments provide a context for higher rates of depressive symptoms in PD, as compared with patients with other chronic disabling conditions matched for disability [28]. Similarly to other medical conditions, reactive mood changes, including demoralization, anxiety, and depression, can develop in response to fears about PD, its impact, and perceived or actual disability [18]. In addition, as in the general population, major life events in patients with PD can contribute to the development of

depression, which is further modulated by coping abilities and social supports [29•]. However, the onset of depressive syndromes and their natural history do not parallel the course of the motor disturbance. The likelihood of a history of depression is two times greater in the immediate “premotor” years before diagnosis of PD [16], providing evidence that the neurodegenerative process contributes to prodromal mood disturbances as the movement disorder also emerges.

Degeneration of dopaminergic neurons and intraneuronal Lewy bodies in the substantia nigra pars compacta are the signature neuropathological lesions of PD. However, it is well known that in PD, neurological disease extends beyond the midbrain, and also involves discrete loss of noradrenergic and serotonergic neurons. Together, these neuronal systems are associated with regulation of mood and reward systems as well as mood disturbances in PD patients and the general population [17•]. A prevailing model for development of depression proposes that degeneration of mesocortical and mesolimbic dopaminergic neurons causes orbitofrontal dysfunction, which disrupts serotonergic neurons in the dorsal raphe and leads to dysfunction of depression-related orbitofrontal-basal ganglia-thalamic circuits [27]. Evidence for reduced dopamine transporter activity, frontal blood flow, and caudate-frontal glucose metabolism in depressed relative to nondepressed PD patients supports this conceptualization [30–33]. These findings are consistent with structural neuroimaging studies associating PD depression with white matter loss in cortical–limbic circuits [34, 35]. Functional neuroimaging studies investigating PD depression implicate dopamine and noradrenergic neuronal dysfunction, plus more prominent cortical cholinergic denervation in the setting of dementia [33, 36] relative to limited evidence clarifying a role for serotonergic dysfunction [37•, 38]. Most studies are limited by their use of correlational analyses with depressive symptoms, rather than comparisons of PD patients with and without depressive disorders [39].

Mood changes occurring in the context of deep brain stimulation (DBS) for treatment of motor dysfunction in PD provide another window for investigating PD depression. Suicide, aggression, depression, and mania are among the affective and behavioral complications after DBS, particular subthalamic stimulation relative to pallidal or thalamic stimulation [40]. Subthalamic stimulation is hypothesized to inhibit serotonergic transmission via interconnections between the substantia nigra pars reticulata, medial prefrontal cortex, and ventral pallidum [41]. Case reports describe acute depressive states on stimulation of the substantia nigra [42, 43]. Spread of the stimulation field to adjacent nonmotor circuits, deviant electrode placement, or activation of inappropriate electrode contacts can also result in stimulation-related mood changes. Modification of the contact selection may resolve mood disturbances in some cases. A dopamine-withdrawal syndrome with prominent depression can develop when antiparkinsonian medications are reduced postoperatively [44•]. In some instances, post-DBS depressive disorders are unrecognized as preexisting conditions, although disappointment with the surgery results also contributes to reactive mood changes, which can evolve into a persistent mood disorder.

Depressive disorders, which may be better phenotypic markers than symptom severity scores, were present at higher rates in unaffected first-degree relatives of patients with PD, suggesting a shared familial susceptibility to PD with depression [45]. Whereas none of the

genetic mutations associated with PD or with depressive disorders have been found to be associated specifically with PD depression, nonmotor symptoms have not been assessed consistently in studies on genetic factors in PD [46]. Two studies showed an association between *LRRK* G2019S mutations and higher depression scores [47, 48]. In a separate study of early onset PD patients, unaffected relatives of probands with compound heterozygous *PARK2* mutations were more likely to have higher depression symptom scores [49], as compared with relatives of probands without *PARK2* mutations. Two earlier studies suggested a relationship between depressive symptoms in PD and serotonin transporter gene polymorphisms [50, 51]. Subsequently, genotype or haplotype associations for the serotonin or dopamine transporter genes have not been observed [52–54], suggesting that these common genetic variables do not play a significant role in the origin of depression in PD.

Clinical Features

Affective disorders, like other medical conditions, are composed of a constellation of signs and symptoms with a generally predictable course, prognosis, and response to treatment. Advanced patient age or the challenges of PD itself may lead to conclusions that depressive disturbances are “understandable.” However, emotional reactions to specific concerns or circumstances, bereavement, and adjustment disorders, which are situational by definition, are generally not regarded as affective disorders as they resolve when the individual adapts to the stressor. Inability to adapt to a stressor, whether related to PD or something else, can be a feature of a clinical depressive syndrome.

Direct inquiry about mood phenomena is critical for detection of depressive disturbances, otherwise these diagnoses are missed [7]. The phenomena of the main subtypes of depressive diagnoses in PD (major depression, minor depression, and dysthymia) are similar to those of depressive subtypes in non-PD populations. Major and nonmajor forms of depression are distinguished by milder and fewer symptoms in the latter. In addition to persistent changes in mood, including the ability to experience pleasure (hedonic capacity), depressive disorders involve prominent somatic signs and complaints, cognitive changes, and vegetative symptoms (disruptions in sleep and appetite) that overlap with the features of PD itself (Table 1). Additionally, PD-specific features (e.g., medication effects on motor and mood states, the context of having a progressive disease for which there is no cure, and the increased occurrence of other psychiatric comorbidities such as impulse control disorders or psychosis) complicate the assessment for a depressive disturbance. Major depressive episodes also occur in patients with bipolar disorder, which can be long-standing before the onset of PD.

Assessment

Many symptoms of depressive disturbances overlap with the physical features of PD (Table 1). To avoid underdiagnosis of PD depression, a National Institutes of Health workgroup recommended an inclusive diagnostic approach in which overlapping somatic features are regarded as features of the depressive disorder and not of PD alone. Separate validation studies support the use of the fourth edition of the American Psychiatric Association’s

Diagnostic and Statistical Manual (DSM-IV) diagnostic criteria for major depression, minor depression, and dysthymia in PD [55].

Assessment and recognition of depression in PD was ranked highly as one of the indicators for improving PD care. [56]. Clinician and self-report rating scales facilitate screening and identification, but are not substitutes for a diagnostic clinical examination [13•]. A number of self-report depression screening tools have favorable psychometric properties in PD patients and are valid predictors of major and nonmajor depression; the choice of a scale may be largely driven by the ease of administration [13•]. Although periodic screening is recommended screening measures alone do not change patient outcomes; enhanced patient care, including involvement of some form of mental health services, is needed to treat the mood disorder. Once a depressive disturbance has been identified, the depression scales can be used to track treatment response at clinical follow-up visits, much as a sphygmomanometer is used to track blood pressure in someone identified as hypertensive. And, just as hypertension can be associated with laboratory abnormalities, patients with PD and depression should undergo a physical examination and laboratory screening to investigate systemic causes of depressive phenomena, e.g., thyroid or liver dysfunction, or testosterone or vitamin B_{12} deficiency. It is also important to evaluate the role of the antiparkinsonian regimen in mood variability, with adjustments made to minimize fluctuations that can be associated with mood lability.

It is also important for clinicians to appreciate that depressive disorders involve a number of phenomena beyond the nine DSM-IV criteria (of which five are somatic and only four are affective). Because of this overlap between PD and depressive somatic symptoms, a focus on emotional rather than neurovegetative symptoms assists with the diagnosis of depressive disorders. Similarly to major depression in the absence of neurological disease, core features of major depression are a persistent and pervasive low mood, diminished ability to enjoy otherwise enjoyable undertakings (anhedonia), or decline in the interest level from the usual baseline [57]. Nondepressed PD patients may limit their usual pursuits (e.g., woodworking) because of motor symptoms, but a depressed PD patient will fail to seek alternative activities to enjoy. Nonsomatic depressive features, such as excessive pessimism, negative ruminations, tearfulness, hopelessness, and guilt, help distinguish depressed from nondepressed PD patients. Some studies indicate that self-blame, negative self-attitude, delusions, and suicidality are less common in major depression in PD patients. However, these phenomena can still be present. Anxiety can be a prominent feature of a depressive disorder, but the co-occurrence of anxiety disorders and PD depression is also common [58]. Similar phenomena occur in nonmajor forms of depression, but with milder and fewer symptoms. Even “subsyndromal” depressive disturbances cause significant suffering.

Difficulty coping can be an important sign of depressive disorders. Successful coping and adaptation are essentially impossible in the face of unremitted mood disorders. Accordingly, diagnosis of a depressive disorder should be considered when self-reported disability and distress exceed what is expected from the clinical examination. Patients or clinicians can be reluctant to consider a depressive diagnosis because of fears of stigma; yet, unacknowledged and untreated psychiatric disturbances are ultimately more problematic. Following treatment of depression, individuals can compensate and face challenges associated with PD, a sign

that the mood disorder is responding to treatment—many patients say, “I can cope with PD, but not when depressed.”

Clinicians should also inquire directly about feelings of hopelessness and helplessness and thoughts of death, suicide, or homicide. Although suicide is reported as uncommon in PD, current suicide ideation is evident in about 11 % of PD patients [59], but does not seem to occur at a greater frequency after DBS surgery [60].

Manic and hypomanic phenomena are not well characterized in PD [61]. Long before PD onset, some patients develop bipolar disorder, a chronic affective disorder characterized by depressive and hypomanic or manic episodes. In PD, isolated manic phenomena most often occur as the result of dopaminergic medications or neurosurgical treatments. Some patients manifest hypomanic features in the “on state” with increased irritability and goal-directed activities. Aside from fluctuating mood states, mania and hypomania occur similarly as in non-PD patients. The features include elevated mood and sense of self, irritability hyperactivity, increased goal-directed activity, including risky behaviors, and mood-congruent psychotic phenomena.

Unique to PD are drug-induced or fluctuating mood states that correspond, to some extent, to “on–off” periods related to antiparkinsonian medications [62]. Patients with levodopa-related motor fluctuations tend to be more anxious than those without fluctuations. In some cases, severe anxiety or panic attacks occur during off periods [63]. “Nonmotor” fluctuations commonly involve panicky states, sadness, or agitation when “off,” but the mood symptoms can persist after motor function improves. Less often, enhanced well-being or hypomanic-like states occur during “on” phases. Severe situational anxiety also aggravates motor deficits, causing motor fluctuations. For example, an individual became anxious about being able to answer the phone, and, although he was in an “on” phase, would become akinetic whenever the phone rang. The dopamine dysregulation syndrome and dopamine agonist withdrawal syndrome also involve frequent severe mood swings [44•].

Clinical Correlates

Studies on clinical correlates of PD depression have yielded a variety of results. The age of onset, severity, duration, stage, or subtype of PD is inconsistently related to when depressive episodes commence or their severity [57]. Reported risk factors for PD depression include motor disability [64], female gender [15], past psychiatric history [65, 66], neuropsychiatric comorbidities [67], predominance of right-sided motor symptoms [68], and greater imbalance and rigidity [69], but others have not confirmed these results [70,71]. Thus, the main risk factor appears to be the underlying disease process of PD itself.

Treatment

Treatment of depressive disturbances is indicated when symptoms persist and contribute to distress or dysfunction. The approach to treatment should be individualized to the patient and should be multidimensional, including *medications* as appropriate, *education* about the mood disturbance and how it relates to PD, facilitation of *skills* to improve strategies to cope with mood symptoms, and emotional *support*. Recent single-site and multi-site randomized

controlled trials (RCTs) of antidepressant medications and cognitive behavioral therapy (CBT) (Table 2) provide evidence of therapeutic options for major and nonmajor depression in PD [77•]. When life stressors are prevailing problems and it is unclear if the patient has a mood disorder, “watchful waiting” and problem-solving strategies are reasonable first steps, with follow-up no later than 2–3 weeks to evaluate the patient for a persistent mood disturbance. Early use of occupational, physical, and speech therapies, home care services, and social workers increases patient and caregiver knowledge of how PD affects them (education), enhances positive disease self-management (skills development), and provides support, potentially reducing the impact of stressors that could become overwhelming and contribute to depressed or anxious moods. Exercise, healthy emotional activities, adequate sleep hygiene, and engagement in peer support programs should also be encouraged.

As seen in the general population, vigorous measurement-based and stepped-care approaches that include multiple medication trials, each lasting several months, plus psychotherapy, may be required to achieve remission [78]. When treated deliberately and assiduously, depressive disorders in PD respond effectively to medications, somatic treatments, psychotherapies, and rehabilitative therapies, or a combination of these [79]. Residual depressive symptoms are often evident despite a significant response to an antidepressant medication or other intervention, indicating that longitudinal monitoring and adjustments in treatment are indicated until the depressive disorder completely remits. Although it is not always possible to eliminate every symptom of depression, a recovery-oriented approach emphasizes individual strengths and resilience, improved function, the pursuit of meaningful goals for that individual, and a sense of hope and optimism. Despite that, patients with PD depression face barriers to mental health care use, including low health literacy, ability to access care, availability of clinicians who are knowledgeable about PD, and a desire for psychotherapy versus medications [10]. Multidisciplinary PD specialist team care is one model that helps overcome some of these barriers and improve outcomes [80•].

Antidepressant Medications

Therapy with antidepressant medications in PD received support from RCTs [72, 74, 81–83]. However, the guidelines from recent evidence-based medicine reviews of pharmaceutical treatment of depression in PD [84] must be interpreted in the context of the criteria used to designate a medication as efficacious. For example, in the most recent review [84], pramipexole is reported as the *only* medication with “sufficient evidence” from clinical trials on which to base efficacy conclusions. It is important to note, however, that the pramipexole studies targeted depressive symptoms, and the effects of pramipexole on depressive disorders were not reported [81]. In addition, since most antidepressant medications were developed in the general population, not in PD samples, evidence from medication trials is more likely to meet the criteria for the designation “likely efficacious” rather than “efficacious,” the highest level.

In general, all traditional antidepressants studied in PD have been found to be safe and well tolerated; efficacy, relative to placebo, has been demonstrated for nortriptyline, venlafaxine extended release, desipramine, citalopram, and paroxetine, although the time course of the

antidepressant response has differed (Table 2). For example, nortriptyline demonstrated superiority to placebo in the short term (i.e., after 8 weeks) [83], and both nortriptyline and paroxetine demonstrated long-term maintenance (i.e., 6 months) of treatment gains [19]. It is critical to recognize the long-term effects of maintenance treatment; antidepressant treatment trials in all populations typically have a prominent placebo response, but the early placebo response is generally not sustained [74]. Most treatment trials last 8–12 weeks and are intended to test the superiority of one intervention versus a comparator. By contrast, in clinical practice, patients are advised to expect changes in symptoms over time, with a full antidepressant response taking up to 12 weeks, followed by continued improvement of any residual symptoms. The intervention is regarded as ineffective for that patient when a response is not observed within 12 weeks *and* the patient has received the maximum indicated doses. When the clinical response is insufficient, medication adjustments are indicated at any stage, including after the initial 12-week trial, and especially if there are indications of reemergent depressive symptoms or relapse.

Initial findings in PD favored use of serotonin–norepinephrine reuptake inhibitors. A subsequent meta-analysis provides support for efficacy and tolerability of SSRIs, as a class, for treatment of PD depression [84, 85]. However, the Study of Antidepressants in Parkinson's Disease, a more recent large blinded trial, demonstrated the efficacy of serotonin–norepinephrine reuptake inhibitors and SSRIs [74]. Concerns that SSRIs worsen parkinsonism are not substantiated [74, 86]. The risks of adverse interactions of SSRIs with monoamine oxidase B inhibitors causing a hypertensive crisis or serotonin syndrome are not supported [87, 88]. Of note, an open-label, randomized, prospective, parallel group study of augmentation of levodopa with selegiline, a monoamine oxidase B inhibitor, showed that it prevented aggravation of minor depression in PD over a 1-year interval [89]. Since anti-depressants can aggravate anxiety, starting doses should be low.

Dopamine agonists have been explored as a primary treatment for PD depression with mixed results [90]. Despite small effect sizes, pramipexole showed efficacy for reducing depressive symptoms over 12 weeks [81]. Randomized, open-label trials of pramipexole also noted antidepressant effects [91, 92]. The results from other blinded trials in PD are inconclusive [93] or negative regarding depression, although mood measures were not the primary outcomes [94]. Alternative treatments such as omega-3 fatty acids [95] and left prefrontal repetitive transcranial magnetic stimulation are being explored in small RCTs, with encouraging results [96–98].

Other Somatic Treatments

In the general population, electroconvulsive therapy (ECT) is indicated for cases of severe depression when a rapid response is needed, such as for depression-related psychosis, catatonia, or severe vegetative symptoms with impending starvation or suicidality. Medication intolerance and failure to respond to antidepressants are also indications for ECT. In PD, ECT is also very effective for depressive disturbances and is also used to treat psychosis that has not responded to other interventions [12, 99]. Some patients require maintenance treatments, e.g., once monthly, in order to maintain treatment gains. Motor symptoms also improve with ECT, even in the absence of a mood disorder. Therefore, it is

not uncommon to see an aggravation of mood and motor symptoms in the days before a maintenance treatment. Vagal nerve stimulation and DBS are being explored as alternatives to other somatic treatments for PD depression [100].

Behavioral Treatments

Psychosocial interventions, such as CBT, have received less scientific attention in PD patients [76, 101], despite demonstrated success in other geriatric [102] and neurological [103] populations. In addition to medication adjustments, CBT can be a first-line or adjunctive treatment for mild-to-moderate depressive disturbances in PD. In a ten-session RCT of CBT for PD depression that included some patients already taking antide-pressants, symptom severity improved by 56 % relative to 8 % for the control group [76]. As compared with usual clinical management, subjects undergoing the CBT protocol, which incorporated behavioral activation, cognitive restructuring, anxiety management techniques, sleep hygiene approaches, and caregiver support, had notable improvements in PD depression over the 14-week period. Additionally, there were significantly more treatment responders in the CBT group (i.e., number needed to treat 2.1; absolute risk reduction 48 %), and large effect sizes were observed on all depression outcome measures. Several uncontrolled pilot trials and case series designs specific to CBT for PD depression produced similar results [77•] as did a ten-session phone-based CBT approach [73]. A small (N=16) randomized study of a 12-session group psychotherapy, incorporating a psychodrama intervention (i.e., role-playing daily situations and discussing their meaning and psychosocial implications) was associated with significant improvements in PD depression over 6 months [101].

Conclusions

Knowledge of the pathophysiology, features, and effective treatments of depression in PD continues to advance. Even with these advances, the greatest challenge in clinical settings with PD patients is recognizing and treating depressive disturbances to the point of remission. The high prevalence of depression in PD warrants a high suspicion for the presence of a mood disturbance along with definitive treatments and ongoing monitoring for clinical response.

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Table 1

Overlapping clinical features of major depression and Parkinson's disease

	Major depression	Parkinson's disease
Motor phenomena	Psychomotor retardation, stooped posture, restricted/depressed affect, agitation	Bradykinesia, stooped posture, masked face/ hypomimia, tremor
Other somatic complaints	Physical complaints, muscle tension, gastrointestinal symptoms, sexual dysfunction	
Vegetative changes	Decreased energy, fatigue, sleep and appetite changes	
Cognitive disturbances	Poor concentration, decreased memory, impaired problem-solving	

Table 2

Randomized placebo-controlled treatment trials for Parkinson's disease depression

Study	Treatment[a]	Diagnosis	Sample size (*N*)	Trial duration	Significant findings regarding reduced depressive symptoms
Devos et al. [72]	Desipramine 75 mg, citalopram 20 mg, placebo	Major depression	48	30 days	14 days after treatment: desipramine > citalopram, placebo. 30 days after treatment: desipramine = citalopram > placebo
Menza et al. [73]	Nortriptyline 64 mg, paroxetine 32 mg, placebo	DSM-IV depressive disorders[b]	52	8 weeks	Nortriptyline > paroxetine, placebo
Richard et al. [74]	Paroxetine 24 mg, venlafaxine extended release 121 mg, placebo	DSM-IV depressive disorders[b,c]	115 (17 sites)	12 weeks	Paroxetine, venlafaxine > placebo
Psychotherapeutic interventions					
Veazey et al. [75]	CBT vs support group	Depressive or anxiety symptom ratings	14	9 weeks	CBT > support group for anxiety symptoms
Dobkin et al. [76]	CBT vs TAU	DSM-IV depressive disorders[b]	80	10–14 weeks	CBT > TAU

CBT cognitive behavioral therapy, *TAU* treatment as usual

[a] Average doses

[b] Major depression, dysthymia, and depression not otherwise specified

[c] Also includes subsyndromal depression