Introduction

Parkinson disease (PD) is a common neurodegenerative disease affecting about 1% of adults aged over 60 years\(^1\). Although PD is primarily a movement disorder, depression in PD (dPD) is one of the most common psychiatric symptoms that complicate the course of the illness. Estimates of the prevalence of depression in patients with PD vary widely from 2.7% to more than 90% because of inconsistent sampling methods and case diagnoses\(^2\). Considering the studies as a whole, the prevalence of dPD is probably from 20% to 45%, with the lower figures relating to community-based studies\(^3\). Patients with dPD have more severe neurologic symptoms than those with PD and no depression, indicating an advanced and widespread neurodegenerative process\(^4\).

Depression appears to be one of the most important factors impairing the quality of life in patients with PD; therefore, evaluating depression in these patients is important\(^5\). Despite the frequency of dPD, there are no uniformly accepted standards for treatment. Most patients go untreated, and half of antidepressant users remain depressed, suggesting that even when delivered, treatment is often inadequate or ineffective\(^6\). There are three main questions concerning the prescribing of an antidepressant. The first is whether an antidepressant can increase or induce parkinsonian symptoms. The second is whether prescribing an antidepressant is safe in a patient with PD. The third is how to choose an appropriate antidepressant for a PD patient with depression and other medical comorbidities.

Screening and Diagnosis of dPD

The gold standard for establishing the diagnosis of depression remains a structured interview using The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). DSM-IV diagnostic criteria for major depression includes the persistent presence of five of the following nine symptoms: depressed mood, diminished interest in activities, significant weight gain or loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or inappropriate guilt, diminished ability to think or concentrate, and recurrent thoughts of death\(^7\). It technically excludes a diagnosis of major depression in PD,
because the depression is “associated with a medical condition.” Nonetheless, the remaining DSM-IV criteria can be used to evaluate and classify the depression⁸. In general, lower prevalences are reported with study designs using DSM-IV criteria.

The majority of patients with PD have non-major depressive syndromes that include minor depression, dysthymia, and subsyndromal depression⁹. These should be taken seriously, because they are of clinical relevance and are usually responsive to treatment. On the other hand, many symptoms of depression (e.g., psychomotor slowing, depressed mood, difficulty concentrating, body weight loss, fatigue, or sleep disturbance) may also be seen in PD without depression, which may cause overdiagnosis in this group¹⁰. The National Institute of Health-sponsored workshop recommended changes to DSM-IV diagnostic criteria for use in dPD¹¹. This report, published in 2005, suggested the following: (1) use an inclusive approach to symptom assessment (count a symptom present regardless of whether it is believed to be related to the underlying PD or depression); (2) omit decreased interest as a core affective symptom when diagnosing minor or subsyndromal depression; (3) carry out assessments in the “on” state for patients with motor fluctuations; and (4) use informants when evaluating cognitively impaired patients.

One helpful tool to assess dPD is to use the time patients spend in the waiting area to fill out one of the many depression rating scales. Rating scales such as the Beck Depression Inventory (BDI), the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS), the Zung Self-rating Depression Scale (SDS), the Unified Parkinson’s Disease Rating Scale Part I, the Cornell Scale for the Assessment of Depression in Dementia, the Center for Epidemiologic Studies Depression Scale, the Hospital Anxiety and Depression Scale (HADS), and the Geriatric Depression Scale (GDS) have been used to assess dPD¹². These can be easily scored by the physician or nurse and can be used not only in the assessment of depression but also to follow patients during treatment. For screening purposes, the HDRS, BDI, HADS, MADRS, and GDS have been used to assess dPD¹². These can be easily scored by the physician or nurse and can be used not only in the assessment of depression but also to follow patients during treatment. For screening purposes, the HDRS, BDI, HADS, MADRS, and GDS have been used to assess dPD¹². For measurement of severity of depressive symptoms, the HDRS, MADRS, BDI and SDS are recommended. It should also be noted that depression scales should be interpreted with caution in the face of cognitive impairment, as their validity is questionable under these circumstances¹⁴. In addition, cut-off scores adjusted for somatic and cognitive comorbidities are required.

The diagnosis of dPD should not be solely made on the basis of a score on a rating scale.

Etiology of dPD

There is no consensus as to whether the etiology of dPD is organic or reactive, or both¹⁵. Evidence against the reactive hypothesis is the relative absence of guilt, shame or sorrow that is associated with dPD and the fact that depression can precede the diagnosis of PD¹⁶,¹⁷. There is a greater degeneration of dopaminergic neurons in the ventral mesencephalon in PD patients who are depressed than in those who are not¹⁸. Although levodopa is helpful in treating depression in a minority of PD patients, most do not exhibit a brisk response to this therapy alone. Depression is also linked to a decrease in the activity of norepinephrine and serotonin. Serotonergic projections from the brainstem raphe nuclei undergo degeneration in PD, which may be a key abnormality in the etiology of dPD¹⁹. Structural brainstem midline alterations have also been detected in both magnetic resonance images and transcranial sonograms in patients with primary depression and in those with dPD, supporting a role of the median raphe nuclei in mood disorders²⁰. Positron emission studies show hypometabolism in the caudate and orbital-inferior frontal lobe, reduced cortical 5-HT₁₅ receptor binding and a reduction in dopaminergic and noradrenergic binding in the limbic system in dPD patients compared with nondepressed PD patients²¹. Noradrenergic dysfunction may also be relevant to dPD given the known pathologic involvement of the locus ceruleus²². The locus ceruleus is the principal noradrenergic outflow system with connections to mesolimbic and mesocortical regions. The organic hypothesis of dPD may, therefore, be explained by dysfunction in the following brain regions, neural networks, and neurotransmitters: (1) subcortical nuclei and the frontal lobes; (2) cortical-striatal-thalamic-cortical and basotemporal limbic neural networks; and (3) serotonergic, noradrenergic and dopaminergic neurotransmission mechanisms.

The natural history of dPD does not parallel the progression of physical symptoms, suggesting that it is an independent process that might affect vulnerable patients. There might be a triphasic relationship between depression and stage of the illness, with higher frequencies of depression occurring at the Hoehn and Yahr stages I and III/IV²³. A distinction between presumed
“organic” and “psychological” etiologies does not contribute to our understanding, nor does it help us with diagnostic or therapeutic decisions, and should therefore be abandoned. A more integrated neuropsychiatric approach to body and mind should be encouraged.

Treatment of dPD—General Considerations

After confirming the diagnosis of dPD, the first step is to initiate a plan to keep the patient safe by asking about suicidal thoughts and about plans that the patient may have for suicide. A long-term plan must then be structured to minimize stress and increase quality of life. Often a psychiatrist, social worker, and occupational therapist can be helpful in this readjustment period. A description of the psychotherapeutic approaches is beyond the scope of this article, but these approaches can be effective alone or in combination with antidepressant drugs, particularly in relation to reactive depressive episodes around the time of diagnosis. Although there is insufficient evidence to support or refute the value of exercise in reducing depression, exercise training has been shown to be beneficial with regards to physical functioning, quality of life, strength, balance and gait speed for PD.

It is widely accepted that higher levels of depression are found during the “off” periods in patients with fluctuating PD; however, the response of depression to long-term treatment with levodopa is generally unsatisfactory. Levodopa is metabolized by catechol-O-methyltransferase (COMT) using S-adenosyl-L-methionine as the methyl donor, which leads to the subsequent formation of homocysteine. PD patients with elevated homocysteine levels have a higher prevalence of cognitive impairment and depression. Studies have found that inhibition of COMT with tolcapone, which has been shown to be helpful in the treatment of major depressive disorder, or entacapone in PD patients results in decreased plasma homocysteine levels. However, tolcapone was banned from the market owing to an increased risk of fulminant hepatitis. To date, no controlled trials of entacapone aimed at assessing antidepressant efficacy in PD have been reported.

Amitriptyline, an antiparkinsonian agent with several pharmacologic mechanisms, is known to ameliorate the motor symptoms of PD. A literature review supported the role of amantadine as an antidepressant. A recently published report showed that joint therapy with an antidepressant and amantadine may be effective in treatment-resistant unipolar depression. It has been shown that the D3 dopamine receptor agonist pramipexole is effective in treating PD and non-PD depression. In one prospective randomized trial, 1 mg or 5 mg of pramipexole per day showed benefits comparable to those of fluoxetine. The evidence for ropinirole, which is also selective for D3 but with less affinity than that of pramipexole, as an antidepressant is limited. In a retrospective review, ropinirole 0.25–1.5 mg daily added to a tricyclic antidepressant (TCA) or selective serotonin reuptake inhibitor (SSRI) was effective and relatively well tolerated. In conclusion, the replacement of dopamine is ineffective or only partially effective in treating dPD patients.

There are several classes of antidepressant agents, including TCA, SSRI, monoamine oxidase inhibitor, serotonin noradrenergic reuptake inhibitor (SNaRI), noradrenergic and specific serotonergic antidepressant (NaSSA), serotonin agonist and serotonin reuptake inhibitor (SARI), noradrenergic and dopaminergic reuptake inhibitor (NaDRI), noradrenaline reuptake inhibitor, amongst others. Until recently, there was insufficient scientific data available to make an evidence-based choice of antidepressants for treatment of dPD. In 2006, the American Academy of Neurology practice parameter on the treatment of depression, psychosis and dementia in PD recommended that the TCA amitriptyline be considered in the treatment of dPD; however, because of its side effect profile, it may not necessarily be the first choice of antidepressant. A Cochrane review of trials of antidepressants for people aged over 55 years concluded that there is no significant difference in efficacy across antidepressant classes, although TCAs have been shown to be associated with a higher withdrawal rate because of side effects. Drug selection for the individual patient should, therefore, depend on coexisting medical conditions, concomitant drug therapy, expected side effect profile of the given antidepressant, and cost of the antidepressant.

Randomized controlled studies concerning the efficacy of TCAs in PD showed that imipramine, nortriptyline and desipramine were effective in treating depression and may even reduce motor symptoms. The anticholinergic and antihistamine effects of TCAs can be beneficial in the treatment of drooling and tremor in PD, and in sedation of agitated patients, respectively. However, the unwanted adverse reactions of anticholinergic
effects may cause dry mouth, blurred vision, urinary retention, cognitive symptoms, or cardiac conduction abnormalities, especially in elderly patients. Although no antidepressant is ideal, many clinicians begin with one of the SSRIs because of their ease of use, safety in overdose, and generally high tolerability to them. A survey from the Parkinson’s Study Group found that 51% of these physicians use SSRIs first when implementing drug therapy, in contrast with the 41% who use TCAs and the 8% who use “other” drugs. The most commonly encountered adverse events with SSRIs are nausea, headache, tremor, sweating, and sexual dysfunction. Theoretically, increased serotoninergic activity may inhibit dopamine release from dopaminergic neurons, which may aggravate the motor symptoms of PD. However, studies in patients with PD have shown that worsening of motor symptoms during SSRI therapy is a rare phenomenon. The SSRI citalopram was observed to improve not only depression but also bradykinesia in patients with PD treated with levodopa. Regarding the potential for drug interactions, citalopram has a much lower potential for interactions than other SSRIs.

In PD patients who are receiving selegiline (a monoamine oxidase B inhibitor), there has been concern that mixing SSRIs with selegiline might precipitate serotonin syndrome. In a large survey, serotonin syndrome was noted in only 0.24% of patients receiving an SSRI with selegiline. Selegiline should not be considered an absolute contraindication to the use of SSRIs. Venlafaxine (a SNaRI) is a useful third-line antidepressant that can be tried if there has been an unsatisfactory response to an adequate trial of two other antidepressants. However, it has not been formally tested in PD patients. Both venlafaxine and SSRIs can cause hyponatremia, serotoninergic effects, and discontinuation syndrome. Cardiotoxicity (tachycardia, hypertension and prolongation of corrected QT interval) is more problematic with venlafaxine than with SSRIs, but it usually causes fewer anticholinergic effects than TCAs.

Trazodone, an SARI that induces a sedating effect, has been used to treat agitated depression without causing significant anticholinergic side effects. Common side effects of trazodone include orthostasis, dizziness, and sedation. Bupropion (a NaDRI) has been reported to induce a modest improvement in motor symptoms in some PD patients. On the other hand, there are some reports of patients treated with bupropion who developed acute dystonia or parkinsonism. It tends to be more “activating” than many other antidepressants and may, therefore, ameliorate fatigue. Common side effects include insomnia, agitation, constipation, dry mouth, excessive sweating, tremor, and weight loss. At high dosages, bupropion may cause psychosis and seizures. Mirtazapine (a NaSSA) has an advantage over other antidepressants in that it decreases anxiety, nausea, and insomnia. This drug is also reported to have a potential additional benefit in the treatment of tremor and levodopa-induced dyskinesias. However, a case series reported four patients with PD who developed sleep-related behavioral problems, including nocturnal confusion, talking during sleep and hallucinations, while taking mirtazapine. In conclusion, antidepressant therapy should be selected on the basis of each individual’s needs.

Treatment of dPD—Individual Patient Considerations

As PD progresses, the severity of depression may change. Antidepressants that are useful early in PD may be less useful later. In addition, medical comorbidity and associated symptoms, such as anxiety, pain, psychosis and sleep disorders, affect the choice of an antidepressant drug. These factors have not been systematically studied and the following should be considered accordingly.

Depressive Patients in Early Stage PD

It is well known that treatment with a dopamine agonist in early stage PD can delay the onset of dyskinesia and motor fluctuations. Preliminary studies have reported the effectiveness of the dopamine agonist pramipexole as an antidepressant in both non-PD and PD populations. It is important to determine whether the combination of a dopamine agonist and an antidepressant is superior to either alone, and whether dopamine agonists offer prophylaxis against the development of dPD. Given the known antidepressant activity of the dopamine agonist pramipexole, initiating treatment with it is reasonable. However, it should be noted that dopamine agonists are more likely to trigger delusions and hallucinations than levodopa in older patients with cognitive changes.
Depressed PD Patients with Nocturnal Sleep Disturbances

Nocturnal sleep disturbances that commonly occur with PD include insomnia, motor symptoms such as restless legs or nocturnal off periods, urinary symptoms, as well as neuropsychiatric symptoms such as vivid dreams, hallucinations or rapid eye movement sleep behavior disorder (RBD)\(^49\). Depression is frequently associated with nighttime wakefulness, including inability to fall asleep or to remain asleep. In patients in whom sleep problems begin following the initiation or increase in dosage of antiparkinsonian medication, a reduction in dose or discontinuation of the medication may be beneficial. Selegiline is usually taken twice daily, and to minimize the stimulatory effect attributed to its amphetamine derivatives, the second daily dose should not be taken after 16:00. For nocturnal off periods, certain treatment strategies provide sustained antiparkinsonian effects. For example, controlled-release formulations of levodopa have been shown to improve nocturnal akinesia, tremor and rigidity, and to increase sleep efficiency, with a reduction in sleep fragmentation\(^50\).

Specific sleep-related pathologies, such as restless legs, periodic limb movements, sleep apnea and RBD, have to be treated according to the standard therapies for these disorders. It is commonly believed that restless legs can be exacerbated by antidepressant agents, thus complicating the treatment of dPD patients. Restless legs can be effectively treated with a dopamine agonist. According to a recently published report, buproprion was shown to be useful in the treatment of patients with both depression and restless legs\(^51\). Diagnosis of RBD currently requires the presence of established clinical criteria; polysomnography is needed to confirm the diagnosis. TCAs are known to precipitate RBD. Levodopa may be very effective in patients with PD and RBD. Clonazepam, when taken nightly, is highly effective in the treatment of RBD, with little evidence of tolerance or abuse.

Patients with insomnia secondary to nighttime confusion or "sundowning," or hallucinations and psychosis, may respond well to atypical neuroleptics, such as clozapine and quetiapine; however, these patients should be monitored for symptoms of adverse effects\(^52\). For insomnia, it is important to have patients practice good sleep hygiene. TCAs can be useful, not only to treat depression and maintain sleep, but also to reduce urinary frequency in some patients. The most sedating to the least sedating in this class of medicines are as follows: doxepin, followed by imipramine, desipramine, and nortriptyline\(^19\). Among SSRIs, paroxetine is the most sedative drug and, therefore, is possibly beneficial for insomnia\(^37\). Trazodone and mirtazapine are also sedating antidepressants and may be used alone. Doses should be started low and titrated slowly to provide a restful night’s sleep without causing sedation the next morning. Zolpidem is a good alternative and, unlike trazodone, is not associated with orthostatic hypotension, although it has not been approved for long-term use.

Depressed PD Patients with Bladder Dysfunction

Bladder dysfunction in PD may take an upper or lower motor neuron form and may involve the sphincter or detrusor, or both. Classically, the upper motor neuron defect will produce an overactive bladder with symptoms of urinary urgency and frequency, while a lower motor neuron defect will produce retention with overflow incontinence if it involves the detrusor, or leakage if it involves the sphincter. The prevalence of urinary disturbances ranges from 27% to 39%\(^53\). The most common complaint is nocturia, followed by frequency and urgency, and symptoms correlate with rigidity severity and with years of evolution of PD\(^54\). The urinary questionnaire allows us to identify the type of bladder dysfunction and to select patients who will benefit the most from medications. An overactive bladder will often respond to anticholinergics, such as oxybutynin and tolterodine. Oxybutynin effectively controls detrusor hyperactivity; however, its anticholinergic side effects limit its use in the elderly and in those with dementia\(^55\). Tolterodine has a more favorable side effect profile than oxybutynin, and it is available in a long-acting formulation\(^56\). Antidepressants with antimuscarinic effects, such as imipramine, nortriptyline and doxepin, may treat nocturia, but should be used with caution because of their side effect profiles. In contrast, an underactive bladder with mild retention and a weak stream may benefit from a muscarinic cholinergic agonist, such as bethanechol. Sphincteric dysfunction with symptoms of urinary incontinence or leakage may be treated with alpha-adrenergic blockers to improve bladder emptying, but the side effect of hypotension often limits its usage\(^57\). PD patients should be referred for urodynamic evaluation if the response to anticholinergics is
Depressed PD Patients with Heart and Vascular Diseases

TCAs are associated with documented adverse cardiovascular effects, including increases in heart rate, orthostatic hypotension and conduction delays. Use of TCAs in patients with heart disease carries a proven increased risk of cardiac morbidity and mortality. Among TCAs, nortriptyline is less likely to cause orthostatic hypotension than amitriptyline or imipramine. The SSRIs appear to be relatively safe and effective treatment options for depression in patients with concomitant ischemic heart disease. According to investigators, SSRIs and SNRIs are first-line antidepressants for moderate to severe depression, especially in patients with coexisting cardiovascular disease, with bupropion and mirtazapine as second-line agents. A large-scale randomized trial suggested that sertraline therapy may very likely improve cardiac outcome. Venlafaxine should not be used in patients with uncontrolled hypertension, and regular blood-pressure monitoring is recommended for all patients taking this drug. However, this hypertensive effect may be desirable in patients with postural hypotension. Trazodone should be used with caution in patients prone to orthostatic hypotension and ventricular arrhythmias.

Depressed PD Patients with Pain Comorbidity

Depression and painful symptoms commonly occur together. The frequency of pain in patients with PD ranges from 30% to 70% according to the literature, and is mainly pain of muscular origin, followed by osteoarticular and neurogenic painful syndromes. Some disorders, such as foot dystonia, restless legs, akathisia and musculoskeletal pain, may represent inadequate levels of dopaminergic stimulation. The aim of drug treatment is to reduce the frequency and duration of “off” states. Positron emission tomography has revealed that the pain threshold is lower in these patients but returns to normal after levodopa administration. When pain occurs with excessive dopaminergic stimulation, it is usually associated with neck/facial dystonia or painful dyskinesia. Reducing the dosage or discontinuing adjunctive drugs, such as selegiline, dopamine agonists and COMT inhibitors, usually is the first step. Levodopa dose reduction may be necessary, but will almost certainly result in increased “off” time. Nonspecific pains not specifically related to dopaminergic medications can be difficult to treat. TCAs are thought to affect pain transmission in the spinal cord by inhibiting the reuptake of norepinephrine and serotonin, both of which influence descending pain pathways. Amitriptyline and its metabolite nortriptyline have the best documented efficacy in the treatment of neuropathic and non-neuropathic pain syndromes. Bupropion and venlafaxine also have proven to be effective in patients with neuropathic pain. Venlafaxine, a centrally acting analgesic, is structurally similar to venlafaxine, sharing both serotoninergic and noradrenergic properties. Just as venlafaxine may be helpful with chronic pain in some individuals, tramadol may possibly exert an antidepressant effect in certain patients, particularly those with chronic pain.

Depressed PD Patients with Anxiety

Anxiety often accompanies depression, and up to 40% of patients with PD may have significant anxiety. SSRIs, such as citalopram, escitalopram and paroxetine, may be effective in treating anxiety and depression in patients with PD. New-generation antidepressants, such as venlafaxine and mirtazapine, may be an alternative choice for patients who are depressed and anxious. Short-term use of benzodiazepines, such as lorazepam, clonazepam or alprazolam, may be beneficial in non-suicidal depressed patients with severe anxiety. Benzodiazepines can be problematic in elderly patients with regard to impairment of arousal, cognition and balance. Beta blockers have been used to lessen tremor in PD and may have a small anti-anxiety effect.

Depressed PD Patients with Psychosis

Psychosis in the form of hallucination or illusion and typically visual, usually occurs in patients with advanced disease who are receiving PD pharmacotherapy. The first step in treatment is to exclude potential medical and environmental causes. Antiparkinsonian medications must be reduced or limited to those that are necessary to preserve motor function. Based on expert
opinion, reduction or discontinuation of medications should be carried out in the following order: anticholinergics, selegiline, amantadine, dopamine agonists, COMT inhibitors, controlled-release levodopa, and immediate-release levodopa. Non-PD medications, such as antimuscarinic agents used for bladder hyperactivity, or anxiolytics can be discontinued as well. Tapering and discontinuing one drug at a time, rather than tapering all of the drugs simultaneously, is recommended. Cholinesterase inhibitors (e.g., rivastigmine) have been shown in open-label studies to reduce psychosis in PD and to improve cognition. In addition to antidepressants, an atypical antipsychotic is usually required. A large number of PD patients have been successfully treated with clozapine. Because quetiapine does not require any blood monitoring and clozapine does, quetiapine has become the initial antipsychotic of choice for most PD experts. Quetiapine appears to be safe in terms of motor functioning, but evidence about its efficacy is not compelling. Other atypical antipsychotics, such as olanzapine and risperidone, have been found to worsen motor function in PD patients.

Body Weight Changes Associated with Antidepressant Use

Patients with PD appear to be at greater nutritional risk. In fact, PD patients were four times more likely to report weight loss greater than 4.5 kg than matched control subjects. Various factors contribute to weight loss in PD. Reduced energy intake and/or increased energy expenditure have been postulated as the cause. The disease itself eventually reduces a person’s ability to chew and swallow. Rigidity, tremor, and levodopa-induced dyskinesia may increase energy expenditure. Depression and cognitive changes can further interfere with normal nutrition. The long-term effect of dopaminergic treatment on body weight is not well known. One study reported that previously untreated PD patients experienced a significant loss of weight 2 years after starting levodopa. In contrast, pramipexole produced a significant weight increase, as well as motor and mood improvement. Adequate nutrition and weight stabilization are important for dPD patients. The body weight of dPD patients should be monitored monthly, and a patient’s nutrition should be supplemented with sufficient amounts of vitamin D and calcium to reduce the risk of hip fractures and to strengthen bone density.

The choice of antidepressant in dPD is based on the condition of the patient and the properties of the antidepressant. Marked weight gain frequently occurs during treatment with most TCAs, while SSRIs may induce weight loss during the first few weeks, although some of them have been shown to induce weight gain during long-term treatment. Among TCAs, nortriptyline has a neutral effect on weight change. Among SSRIs, paroxetine seems to be most prone to cause weight gain, whereas citalopram may not produce significant changes in body mass. New-generation antidepressants have been associated with various patterns of change. Venlafaxine does not appear to cause weight changes. Mirtazapine may be placed between the SSRIs and the TCAs in terms of relative risk of weight gain, and bupropion may be the only modern agent to lower weight.

Depressed PD Patients Resistant or Refractory to Antidepressants

The most common cause of failure in treating depression is not the 2–3 weeks it takes for the drugs to have an effect, or the use of too low a dose. The most common cause of failure is related to side effects. Patients with comorbid anxiety disorders may be especially prone to side effects of medications, leading to noncompliance.

Medications should be used at sufficient doses and over sufficient time to treat depression successfully and to prevent recurrences. As a general guideline, if patients are partial responders at 6 weeks, they will likely be full responders by 12 weeks. Thus, changing medication is not indicated in this context. However, if patients are only partial responders at 12 weeks, switching to a new agent is advised. Two broad treatment options exist for switching antidepressants for depressed patients who fail to respond to a SSRI: either a second course of SSRI therapy or a different class of antidepressants. Recently, a meta-analysis of four clinical trials showed that patients who switched to a non-SSRI antidepressant (bupropion, mirtazapine, venlafaxine) were more likely to experience remission than patients who switched to a second SSRI.

For PD patients who are suicidal, have severe treatment resistance or are unable to wait for a response to antidepressants, electroconvulsive therapy (ECT) should be considered. ECT can be effective in alleviating depressive symptoms and has been shown to have at
least short-term benefits in alleviating motor symptoms in PD patients. These gains are not without complications, which should be carefully weighed against the benefits. Repetitive transcranial magnetic stimulation (rTMS) uses an electric coil to generate magnetic fields that stimulate the cerebral cortex. It is very well tolerated by patients and, in contrast to ECT, does not require the use of anesthesia and does not appear to cause seizures or cognitive deficits. Given the results of published studies, high-frequency rTMS applied to the left dorsolateral prefrontal cortex or low-frequency rTMS applied to the right hemisphere seems to be effective in alleviating mood symptoms in PD, and may result in cognitive and motor function improvement. The drawbacks of rTMS include a short-lived therapeutic effect, a muscle tension-type headache at the site of stimulation, and a risk of seizures. At present, the use of rTMS in major depression and in dPD is still considered investigational, and there is still no standard protocol for the selection of the region, or intensity and frequency of stimulation. Additional comparative studies are warranted.

Conclusion

Depression appears to be a common but under-recognized and undertreated symptom of PD. Early recognition of depression is essential for the care of patients with PD, and the importance of a multidisciplinary approach cannot be overemphasized. Further research is needed to improve the diagnostic accuracy for dPD in order to more closely match clinical presentations. Standardized rating scales with proven validity in dPD can be useful to identify and to follow the severity of depression. Presently, there are no established first-choice antidepressant drugs for dPD, and, therefore, the selection of an antidepressant will be largely driven by the differences in the side effect profiles of the available drugs and coexisting medical conditions of the patient. Available clinical evidence is primarily from open trials, which show that TCAs and SSRIs are both effective treatments. There is limited evidence that dopamine agonists may be effective as augmenting agents. It is clear that larger randomized controlled trials are needed to further evaluate the efficacy of antidepressant treatments and to allow for the development of evidence-based treatment guidelines.

References


