TREATMENT IN PSYCHIATRY

Management of Depression in Parkinson's Disease

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Although traditionally considered a purely motor disorder, Parkinson's disease is increasingly recognized as a complex disease process with diverse neuropsychiatric complications in addition to its motor symptomatology. The range of neuropsychiatric complications associated with Parkinson's disease is broad and includes depression, anxiety, apathy, psychosis, cognitive impairment, impulse control disorders, and sleep disturbances. These neuropsychiatric complications become increasingly prevalent over the course of the disease and are often associated with poorer quality of life, increased disability, worse outcomes, and greater caregiver burden (1). As mental health providers commonly encounter depression in the Parkinson's disease population, it is important to be familiar with available, validated treatment options for this illness.

A trial of citalopram was begun in an elderly man with a history of Parkinson's disease with depression and suicidal ideation.

A 68-year-old man with a 4-year history of Parkinson's disease stable on levodopa and no previous psychiatric history was brought by his wife to the emergency department for worsening depression and suicidal ideation. Screening laboratory tests and chest x-ray were unremarkable. Per neurology consultation, the patient was at his baseline with respect to motor symptoms with no new neurological deficits. A head CT had recently been obtained, and repeat imaging was not indicated. He was subsequently admitted to the psychiatry service for management of his depressive symptoms. On admission, he was started on citalopram, which was slowly titrated to a maximum daily dose of 20 mg without any worsening of motor symptoms. Over the next 2 weeks, he reported improved mood without any further suicidal ideation. He was discharged home with outpatient psychiatry follow-up.

PARKINSON'S DISEASE AND DEPRESSION

Parkinson's disease is a chronic, progressive neurodegenerative disorder clinically diagnosed by a combination of cardinal motor signs: bradykinesia, resting tremor, rigidity, and postural instability. The pathological hallmarks of Parkinson's disease include the loss of dopaminergic neurons within the substantia nigra and the presence of Lewy bodies, intracytoplasmic inclusions comprised mainly of alpha-synuclein (2). While the estimated prevalence for Parkinson's disease has varied widely, a recent meta-analysis reported the worldwide prevalence to be approximately 0.3% in the general population, suggesting that there are 7.5 million people living with the disorder worldwide (3). The incidence has been found to rapidly increase in populations over 60 years of age, with a mean age at diagnosis of 65 years (2). A male predominance has also been observed in many but not all epidemiologic studies, suggesting that men may have a higher risk for developing the disease than women (3).

Among the neuropsychiatric complications of Parkinson's disease, depression is one of the most common and is associated with increased disability and reduced quality of life. Depending on diagnostic criteria used, the estimated prevalence of depression in Parkinson's disease has varied widely across studies, from 2.7% to more than 90%, with an average prevalence of about 35% (4). Factors that have been found to be consistently correlated with depression in Parkinson's disease include early-onset, advanced progression of the disease, "atypical" parkinsonism, female gender, and a personal or family history of depression, as well as psychiatric comorbidities, including anxiety, apathy, psychosis, cognitive impairment, and insomnia (1). While the underlying mechanism remains unclear, depression in Parkinson's disease is thought to result from a complex interaction of psychological, social, and neurobiological factors. For some patients, depressive symptoms may actually represent a prodromal syndrome presenting before motor symptoms become apparent (5). Although depression is common in the disease and increasingly recognized as adversely affecting disability and quality of life, depression in Parkinson's disease remains under-recognized and undertreated in clinical practice (4).

EVALUATION OF DEPRESSION IN PARKINSON'S DISEASE

Recognizing depressive symptoms in Parkinson's disease can be challenging because the psychomotor slowing and blunted affect commonly seen in depression can resemble the bradykinesia and masked facial expression of Parkinson's disease. Additionally, somatic features of depression such as decreased appetite, low energy, and sleep disturbances are commonly seen in patients with Parkinson's disease who do not have depression. Furthermore, depression must be differentiated from apathy, which commonly occurs in Parkinson's disease, is characterized by diminished motivation, and has significant overlap with depressive symptoms. A potentially useful discriminating feature is mood, which is negative in depression and neutral in apathy (6). It is important to remember that the differential diagnosis for depression is broad and in-

cludes other psychiatric disorders such as bipolar disorder, cognitive disorders, neoplastic processes affecting the central nervous system, metabolic and endocrine abnormalities, infections, hypoxemia, sleep disorders, medication side effects, and substance use, as well as hypoactive delirium caused by a variety of underlying illnesses.

The initial assessment of patients with Parkinson's disease presenting with depressive symptoms should involve a comprehensive medical and psychiatric history, review of current medications, collateral information, and physical examination. Screening laboratory tests should include blood cell counts, complete metabolic panel, thyroid-stimulating hormone, and vitamin B12. Depending on the degree of clinical suspicion for other etiologies, such as substance use, sexually transmitted infections, and/or delirium, it may be necessary to check blood alcohol level, blood/urine toxicology, screens for HIV and syphilis, arterial blood gas, and chest x-ray. Head imaging, neurology consultation, and neuropsychological testing should also be considered as clinically indicated (see Table 1).

Once other etiologies have been considered and appropriately ruled out, a diagnosis of depression can be made clinically based on symptomatology. According to a 2008 study by Starkstein et al. (7), DSM-IV diagnostic criteria for major depressive disorder and dysthymic disorder have been validated for use in patients with Parkinson's disease, while the categories of minor and subsyndromal depression likely need further validation for use in this patient population.

TABLE 1. Management of Depression in Parkinson's Disease

Evaluation
• Comprehensive medical and psychiatric history.
• Review of current medications.
• Physical examination.
• Collateral information.
• Laboratory testing to rule out medical etiologies.
• Head imaging, neurology consultation, and neuropsychological testing as clinically indicated.
Diagnosis
• DSM-IV diagnostic criteria for major depression and dysthymic disorder have been validated for use in this patient population (7).
Pharmacologic treatment
• No clear consensus regarding antidepressants for the treatment of depression in Parkinson's disease exists at this time.
• There is some evidence to support the use of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase type B inhibitors (MAOBIs), tricyclic antidepressants, and dopamine agonists (9–13).
• SSRIs remain the most commonly prescribed antidepressants given their more favorable side-effect profile; however, the strength of evidence for the efficacy of antidepressants in treating depression in Parkinson's disease is controversial (1, 4, 8).
• MAOBIs and tricyclic antidepressants may be used cautiously for patients who have not responded to treatment with SSRIs and/or SNRIs (12, 15).
Non-pharmacologic treatment
• There is insufficient evidence to support the efficacy of either ECT or transcranial magnetic stimulation; however, these treatments may be considered in severe, refractory cases that have failed pharmacotherapy (16).
• Psychotherapy, particularly cognitive-behavioral therapy, is increasingly being studied with promising results (10).

MANAGEMENT OF DEPRESSION IN PARKINSON'S DISEASE

Pharmacologic Management

At this time, there is no clear consensus regarding the use of antidepressants for the treatment of depression in patients with Parkinson's disease. There is some evidence to suggest that selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase type B inhibitors (MAOBIs), and tricyclic antidepressants may be effective pharmacologic agents for treating depression in Parkinson's disease. However, the strength of evidence for the efficacy of antidepressants in treating depression in this patient population is controversial. According to a meta-analysis comparing the use of SSRIs and placebo for the treatment of depression in Parkinson's disease, there was insufficient evidence to reject the hypothesis of no difference in efficacy between SSRIs and placebo (8).

The antidepressants with the most evidence for treating depression in Parkinson's disease include citalopram, sertraline, paroxetine, fluoxetine, venlafaxine, amitriptyline, nortriptyline, and desipramine (9–11) (see Table 2). In addition to the role of MAOBIs in treating motor symptoms of Parkinson's disease, a recent randomized double-blind, placebo-controlled multicenter trial (ADAGIO study) showed that rasagiline in combination with antidepressant therapy was well tolerated and associated with reducing worsening of depression in patients with Parkinson's disease (12). There is also some evidence to support the use of dopamine agonists, pramipexole and ropinirole, for the treatment of depression in the disease (9, 10, 13). Despite limited evidence and the lack of formalized treatment guidelines, SSRIs remain the most commonly prescribed antidepressants for the treatment of depression in Parkinson's disease given their more favorable side-effect profile (4).

While SSRIs are generally well tolerated, there is concern that SSRIs may aggravate motor symptoms in patients with Parkinson's disease. However, clinical experience and open-label studies have suggested relatively good tolerability of SSRIs with low incidence of worsening motor symptoms in this patient population (1, 4). Additionally, as MAOBIs are commonly prescribed

TABLE 2. Pharmacologic Agents for Treating Depression in Parkinson's Disease

Medication Class	Dose Range (mg/day)	Side Effects for Medication Class	Contraindications for Medication Class
Selective serotonin reuptake inhibitors	Fluoxetine: 10–60 mg/day Citalopram: 10–40 mg/day *(10–20 mg/day in poor CYP2C19 metabolizers and patients older than 60 years old.)* Sertraline 25–200 mg/day Paroxetine 10–50 mg/day	Common: Gastrointestinal side effects[a], sexual dysfunction, insomnia Rare/serious: Induction of mania, activation of suicidal ideation	Caution with other serotonergic agents due to risk of serotonin syndrome
Serotonin norepinephrine reuptake inhibitors	Venlafaxine: 37.5–225 mg/day Duloxetine: 20–120 mg/day	Common: Gastrointestinal side effects[a], sexual dysfunction, insomnia, dose-dependent increased blood pressure Rare/serious: Induction of mania, activation of suicidal ideation	Caution with other serotonergic agents due to risk of serotonin syndrome
Monoamine oxidase type B inhibitors	Rasagiline: 1–2 mg/day *(hepatic dosing: 0.5 mg/day for mild impairment; avoid use in moderate-severe impairment)*	Common: Nausea, headache, orthostatic hypotension, dyskinesia Rare/serious: Hypertensive crisis, impulse control disorders, paranoia, hallucinations, confusion, sudden sleep episodes, increased risk of melanoma	Caution with other serotonergic agents due to risk of serotonin syndrome Caution with rapid dose reduction or discontinuation due to risk of neuroleptic malignant syndrome-like reactions Contraindicated with concomitant use of other MAOIs (including selective MAOBIs), meperidine, methadone, propoxyphene, or tramadol within 14 days of rasagiline or concomitant use with cyclobenzaprine, dextromethorphan, or St. John's wort
Tricyclic antidepressants	Amitriptyline: 25–300 mg/day Desipramine: 25–200 mg/day Nortriptyline: 25–150 mg/day	Common: Anticholinergic side effects[b], weight gain, dizziness, orthostatic hypotension, sexual dysfunction Rare/serious: QTc prolongation, cardiac arrhythmias, sudden death, induction of mania	Caution with other serotonergic agents due to risk of serotonin syndrome Contraindicated in the acute recovery phase following a myocardial infarction, in patients with a history of QTc prolongation or cardiac arrhythmia, or uncompensated heart failure
Other	Mirtazapine: 7.5–45 mg/day	Common: Sedation, increased appetite, weight gain, elevated cholesterol Rare/serious: Induction of mania, activation of suicidal ideation	Caution with other serotonergic agents due to risk of serotonin syndrome
	Bupropion: 100–450 mg/day	Common: Nausea, weight loss, anxiety, agitation, insomnia Rare/serious: Seizure, induction of mania, activation of suicidal ideation	Contraindicated in patients with a history of seizures, anorexia, bulimia, or undergoing abrupt discontinuation of ethanol or sedatives
Dopamine agonists	Pramipexole: 1–3 mg/day	Common: Nausea, dyskinesia Rare/serious: Impulse control disorders, paranoia, hallucinations, confusion	Caution if renal impairment

[a] Gastrointestinal side effects include decreased appetite, nausea, diarrhea, constipation, and dry mouth.
[b] Anticholinergic side effects include sedation, dry mouth, constipation, urinary retention, and blurred vision.

for the treatment of motor symptoms in Parkinson's disease, there is concern for precipitating serotonin syndrome when MAOBIs are used in combination with SSRIs and/or other antidepressants. Although several studies have found this adverse event to be infrequent, cases of severe, sometimes fatal, serotonin syndrome have been associated with concurrent MAOBI and antidepressant treatment, suggesting that caution be used when prescribing combination therapy in this patient population (STACCATO study) (14).

When beginning pharmacotherapy for depression in a patient with Parkinson's disease, the choice of antidepressant should be based on an assessment of potential benefits versus potential side effects for the individual patient. In general, it is reasonable to start with an SSRI given the decreased risk of adverse events for SSRIs compared to other antidepressants. While the anticholinergic side effects of tricyclic antidepressants may be particularly troublesome in this patient population, a tricyclic antide-

KEY POINTS/CLINICAL PEARLS

- Among the neuropsychiatric complications of Parkinson's disease, depression is one of the most common and is associated with increased disability and reduced quality of life.
- The initial evaluation of patients with Parkinson's disease presenting with depressive symptoms should include a comprehensive medical and psychiatric history, review of current medications, collateral information, physical examination, and laboratory testing to rule out medical etiologies.
- There is no clear consensus regarding choice of antidepressants for the treatment of depression in Parkinson's disease at this time. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed due to their more favorable side-effect profile. Serotonin norepinephrine reuptake inhibitors (SNRIs) may also be considered. Monoamine oxidase type B inhibitors and tricyclic antidepressants may be used cautiously in patients who have not responded to treatment with SSRIs and/or SNRIs.
- ECT or repetitive transcranial magnetic stimulation may be considered in severe, refractory cases that have failed pharmacotherapy. Psychotherapy, particularly cognitive-behavioral therapy, is increasingly being studied with promising results.

pressant may be an appropriate option for patients who have not responded to treatment with SSRIs and/or SNRIs (15).

Non-Pharmacologic Management

Non-pharmacologic interventions, including ECT and repetitive transcranial magnetic stimulation (rTMS), are being explored for the treatment of depression in Parkinson's disease. Thus far, there is insufficient evidence to support the efficacy of either ECT or rTMS for depression in this patient population; however, ECT and/or rTMS may be considered in severe, refractory depression that has failed pharmacotherapy (16). Finally, psychotherapy is increasingly being studied with promising results. According to a recent meta-analysis, cognitive-behavioral therapy appears to be a safe and efficacious treatment for depression in patients with Parkinson's disease; however, further studies are needed to establish the magnitude of this treatment effect (10).

CONCLUSIONS

Although traditionally considered a purely motor disorder, Parkinson's disease is increasingly recognized as a complex disease process with a wide array of neuropsychiatric complications. Depression is one of the most common neuropsychiatric complications of Parkinson's disease; however, the current evidence guiding the treatment of depression in the disease is limited. Given the potential negative impact on motor disability and quality of life, it is important that clinicians consider and treat depression in patients with Parkinson's disease. Further research is required to assess the efficacy and safety of both pharmacologic and non-pharmacologic treatments in order to better inform our management of depression in this disease.

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