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Neuropsychiatric Complications of Parkinson's Disease Treatments: The Importance of Multidisciplinary Care

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Abstract

While Parkinson's disease (PD) is defined clinically by its motor symptoms, it is increasingly recognized that much of the disability and worsened quality of life experienced by patients with PD is attributable to psychiatric symptoms. The authors describe a model of multidisciplinary care that enables these symptoms to be effectively managed. They describe neuropsychiatric complications of PD itself as well as pharmacological and neurostimulation treatments for Parkinsonian motor symptoms, and discuss the management of these complications. Specifically they describe the clinical associations between motor fluctuations and anxiety and depressive symptoms, the compulsive overuse of dopaminergic medications prescribed for motor symptoms (the dopamine dysergulation syndrome) as well as neuropsychiatric complications of these medications including impulse control disorders, psychosis, and manic syndromes. Optimal management of these problems requires close collaboration across disciplines because of the potential for interactions among the pathophysiologic process of PD, motor symptoms, dopaminergic drugs, and psychiatric symptoms. The authors emphasize how their model of multidisciplinary care facilitates close collaboration among psychiatrists, other mental health professionals, neurologists, and functional neurosurgeons and how this facilitates effective care for patients who develop the specific neuropsychiatric complications discussed.

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Keywords

Parkinson Disease; Multidisciplinary care; Neuropsychiatric (symptoms); nonmotor (symptoms); dopamine replacement therapy (DRT); depression; anxiety

Parkinson's disease (PD) is a progressive disorder associated with significant disability and lower quality of life.(1,2) It is diagnosed clinically by its motor symptoms, which include bradykinesia and at least one of tremor, rigidity, or postural instability. These cardinal features of PD are caused by degeneration of dopamine-producing cells in the midbrain. An understanding of this pathophysiology has led to several effective treatments for PD including the dopamine precursor levodopa and dopamine receptor agonists such as pramipexole. Surgically implanted deep brain stimulators (DBS) that target the subthalamic nucleus (STN) or globus pallidus interna (GPi) are also effective at treating motor symptoms. While these treatments address motor symptoms, it is increasingly recognized that much of the disability and worsened quality of life experienced by patients with PD is attributable to neuropsychiatric and other non-motor symptoms.(3,4)

Due to the broad range of symptoms experienced by PD patients and the varied sources of disability associated with this disease, it has become increasingly recognized that the optimal treatment model involves a multidisciplinary approach.(5,6,7) Physicians with multiple specialties, as well as different types of non-physician allied health workers all have important roles to play.(8) Multidisciplinary care not only involves different specialists addressing different aspects of a patient's presentation, it also must involve mechanisms to ensure that these specialists work together as part of a team.(6) It is also important that patients and their carers are involved in prioritizing the issues most in need of clinical attention.(7,8)

We describe an approach to managing neuropsychiatric complications of PD that utilizes a coordinated multidisciplinary PD center with specialized inpatient and outpatient services. We discuss several such complications including anxiety and depressive symptoms, problematic overuse of dopaminergic medication (the “dopamine dysregulation syndrome”), and several psychiatric syndromes that sometimes emerge as a result of treatment with dopaminergic medication including impulse control disorders (ICDs), psychosis and mania. There is a close interrelationship between the motor symptoms of PD, the treatments prescribed to alleviate these symptoms and the development or exacerbation of neuropsychiatric problems. Therefore, the most important intervention for addressing the range of neuropsychiatric problems that occur in PD patients is the establishment of a framework for close collaboration across disciplines.

A multidisciplinary approach to psychiatric complications of PD

In the clinic where Mr. W received his treatment (The Johns Hopkins Parkinson's & Movement Disorder Center), each patient is assigned to movement disorder specialist neurologist as well as a nurse coordinator with expertise in PD. The patient is evaluated for the presenting chief complaint and also screened for a range of motor and non-motor problems, including neuropsychiatric issues that occur with increased prevalence in PD.

Based on this evaluation and screening a coordinated plan of care is drafted that combines the resources of four disciplines – neurology, neuropsychiatry, neuropsychology, and functional neurosurgery. Cases are then reviewed by the multidisciplinary team in a monthly in-person collaborative meeting. Typically these meetings start with a presentation of the case history and, when appropriate, a video examination and review of test results relating to the main issues. Each discipline gives a summary of their individual evaluation of the case and then the movement disorder neurologist moderates a multidisciplinary discussion of the best approach to further evaluation or treatment. This multidisciplinary team also meets monthly with a neuropathologist to review clinicopathologic correlations at autopsy in patients who were followed longitudinally either in clinic or through research protocols.

In this team, the neurologist is best positioned to assess the patient's motor functioning, and to suggest which treatment approaches are most likely to appropriately address motor symptoms. The neuropsychiatrist is able to make psychiatric diagnoses and prescribe psychotropic drugs, and works closely with the neurologist to minimize the use of medications that may be causing or worsening psychiatric illness. The neuropsychologist is able to provide formal assessments of mood states and cognition, especially subtle changes in executive dysfunction that often lead to medication errors, impulsive behaviors, and disinhibition.(9) In some cases, other mental health professionals are called in to help design and implement behavioral psychotherapeutic interventions to address problems such as ICDs that emerge during treatment for PD. In advanced PD, or in patients with less advanced disease who have difficulty tolerating dopaminergic medications, a neurosurgeon with experience implanting DBS devices can help determine when a patient is an appropriate candidate for such a device. The nurse coordinator follows each patient and works with the other members of the treatment team to coordinate care, solicit input from the patient and carers regarding treatment priorities and to ensure that the patient has access to each needed medical specialist and non-physician provider. Other allied health professionals are often involved in the care of patients through this clinic, including occupational therapists, physical therapists and speech and language pathologists.

For patients who develop neuropsychiatric complications that pose a risk to their safety or that otherwise cannot be adequately managed as an outpatient, there is an inpatient neuropsychiatry unit with four beds reserved for patients with PD. While the primary team on this service is psychiatry, these patients are also followed by neurologists with expertise in PD. Consultation with other medical specialists is common, as is consultation with non-physicians health professionals. The nursing staff, as well as the physical therapists, occupational therapists and speech and language pathologists who work on this unit have all received specialized training in working with patients with PD.(10) Thus, our model provides access to multidisciplinary treatment teams in both outpatient and inpatient settings. We now describe how this model serves the needs of patients who experience several common neuropsychiatric complications of PD.

Depression and anxiety associated with motor fluctuations

Depressive and anxiety disorders occur frequently in PD and have a substantial impact on patients' quality of life.(11) The point prevalence of major depression in PD is 17%,(12)

while 31-43% suffer from an anxiety disorder.(13,14) The diagnosis of these disorders is complicated because many PD patients have clinically significant episodic anxiety disorders (e.g. symptoms of panic, social phobia, agoraphobia) that do not meet the threshold for any individual DSM diagnosis but cause substantial distress or disability(15). Diagnosis is also complicated by overlap with other symptoms of PD, which have similar presentations. For instance, autonomic dysfunction, which occurs in many PD patients can mimic or precipitate anxiety attacks.(16) Hypomimia (reduced facial expressiveness) and voice changes can at times be difficult to distinguish from neurovegetative symptoms of depression.(17) Thus, the workup of presentations that appear concerning for depressive or anxiety disorders often requires input from the patient's neurologist and formal neuropsychological testing in addition to a neuropsychiatric evaluation. A multidisciplinary framework for patient care can help ensure that an appropriately broad differential diagnosis is considered.

Many patients with moderate to severe PD experience motor fluctuations that are sometimes associated with anxiety or dysphoric moods.(18) Motor fluctuations refer to changes in motor symptoms over the course of several hours as the effectiveness of dopaminergic medications (e.g. levodopa) diminishes. Often motor symptoms worsen as the patient's last dose wears off before the next dose is taken and absorbed. These are referred to as motor “off periods.” Some patients also experience hyperkinetic and difficult to control movements referred to as dyskinesias when their dopaminergic medications are dosed too high or as a side effect of long-term treatment with levodopa. Many patients, including Mr. W, report worsening mood or anxiety in association with motor off periods, and in some patients anxiety also occurs with dyskinesias.(19) The association between wearing off and anxiety or low mood has been demonstrated to have a dose-response relationship in studies using intravenous infusions of levodopa.(20) Off-periods likely cause anxiety directly through withdrawal of dopamine, but also indirectly – as the patient's motor symptoms return they often become more self-conscious and worry about freezing or being more disabled in public.

A careful history and close observation are necessary to clarify whether a relationship exists between motor fluctuations and anxiety symptoms. While standard treatments for depressive and anxiety disorders are often effective, when there is a clear relationship between a particular motor state and mood/anxiety symptoms, improving motor fluctuations can be a critical component to addressing these psychiatric symptoms. Thus, while a patient's neurologist is best qualified to evaluate the objective severity of their motor symptoms, in patients with associated mood or anxiety symptoms, neuropsychiatric evaluation also plays an important role in determining when their anti-Parkinson medication regimen needs adjusting. Often, if the relationship between anxiety attacks and motor fluctuations is not completely clear we will ask patients to keep a diary that records when their neuropsychiatric symptoms occur in relationship to their PD medication schedule. We ask them to note whether they had missed or delayed a dose (suggesting a more severe off-period) or taken an extra dose (possibly associated with dyskinesias or a hyperdopaminergic state). Once such an association is identified adjustments can be made to reduce the severity and frequency of fluctuations. The addition of a dopamine agonist is one evidence based strategy for doing this.(21) In the case of Mr. W, identifying this association contributed to

the decision to add pramipexole to his regimen, which reduced the severity of his motor off periods and resulted in improvement in his panic symptoms.

As PD advances it becomes increasingly difficult to find a treatment regimen that minimizes both off-periods and dyskinesias. In patients where medications are ineffective at reducing motor fluctuations or cause intolerable side effects, neurosurgical options including STN DBS, GPi DBS, and pallidotomy are all efficacious.(21) Identifying a relationship between fluctuating motor symptoms and neuropsychiatric symptoms can also lead to effective psychotherapeutic interventions to help patients tolerate the discomfort associated with their motor symptoms. Thus, neuropsychiatrists, psychologists, neurologists and neurosurgeons all have important roles to play in diagnosing and treating anxiety symptoms related to motor fluctuations. In our experience, coordinated care by a multidisciplinary team is invaluable for effectively treating these patients.

Dopamine dysregulation syndrome

Another important neuropsychiatric syndrome in PD patients is the dopamine dysregulation syndrome (DDS), which refers to an addictive pattern of dopaminergic drug use with self-administration at doses in excess of those required to control motor symptoms. It occurs in approximately 3-4% of patients.(22) This phenomenon is more common with levodopa, but also occurs with dopamine agonist medications.(23) The overuse of dopaminergic medications is usually associated with other neuropsychiatric symptoms including psychosis, impulsivity and rapid fluctuations between mood states.(23) It is these co-occurring psychiatric problems that often bring patients to clinical attention. Thus, management of this complication is again at the interface of neurology and psychiatry and involves removing opportunities for the patient to overuse medication while also treating co-occurring neuropsychiatric symptoms.

In order to help a patient who has been overusing prescribed dopaminergic medication it is often necessary to facilitate communication among all physicians caring for the patient, as well as their family and other carers.(24) Identifying and describing the specific phenomena driving an individual's pathologic overuse of dopaminergic medication (pursuit of euphoria vs. avoidance of dysphoria) is also important in developing an effective treatment plan in a given patient. For example, Okai et al(25) describe how they use a cognitive behavioral approach to help patients who are overusing medications as a means of addressing anxiety in anticipation of a motor-off period. They describe how some patients will misinterpret sensations that reflect physiologic states (such as fatigue or muscle tension) as instead being related to PD and that by helping patients develop alternative (and more accurate) interpretations of these sensations the anxiety that leads to medication overuse is lessened. In patients with more advanced motor symptoms, the presence of DDS may become an important factor motivating the decision to undergo surgical implantation of a deep brain stimulator which can be very effective at reducing motor fluctuations.(24) In Mr. W 's case, there was a close association between the compulsive overuse of a dopamine agonist and the development of a manic episode. Implantation of a DBS ultimately allowed his motor symptoms to be adequately managed without dopamine agonist medication, which removed opportunity to continue to overuse it.

Impulse control disorders in patients with PD

Although Mr. W 's presentation was consistent with mania, several of his behavioral symptoms, for example his hypersexuality and risky financial decisions, would, in isolation be suggestive of an impulse control disorder (ICD). ICDs refer to pathologic difficulty regulating behavior that leads to hedonic reward, and that lead to negative consequences in excess. In addition to uncharacteristic hypersexual behavior and compulsive buying, other ICDs commonly seen in PD include pathologic gambling and binge eating.(26) ICDs occur in approximately 14% of patients with PD and appear to be driven by the dopamine replacement therapies used to treat motor symptoms.(27) They are substantially more prevalent in patients treated with dopamine agonists such as pramipexole compared to those treated only with levodopa (17% vs. 7%).(21) ICDs that emerge during treatment with dopaminergic medications often are not recognized by the patient as being problematic until they have wrought substantial negative consequences on the patient's relationships or financial well-being.(28) Furthermore, even when patients themselves recognize that there is a problem, shame associated with these behaviors presents a barrier to discussing them with caregivers or clinicians. Thus, especially in patients treated with dopamine agonists, there is value in proactively screening for ICDs. It is also especially important to seek out collateral informants when evaluating for ICDs as caregivers often recognize the existence of a problem before patients themselves.(29)

ICDs in PD are generally caused by treatments prescribed for motor symptoms, therefore appropriate management requires close collaboration between the patient's neurologist and mental health professionals. Neuropsychological testing can be especially important in patients with ICDs to detect subtle changes in executive functioning that may be contributory. Once a drug-associated ICD is recognized, the first step in management is to taper and discontinue the offending medication. Failure to tolerate dopamine agonists due to development of an ICD may contribute to a decision to surgically implant a DBS in order to bring relief from motor symptoms without dopamine agonists. At least in the case of isolated ICDs (without other symptoms suggestive of a manic syndrome), there is little evidence to support the use of mood stabilizers or antipsychotic medications.(30) Even reducing or eliminating the medication that precipitated an ICD may not lead to the cessation of the problematic behavior once it has become habitual. Behavioral psychotherapy is effective (31) and in our experience is often necessary. Some patients also find twelve-step programs helpful to learn to avoid triggers and prevent relapses to problematic behaviors. As with diagnosing ICDs, treating ICDs effectively requires close coordination with the patient's caregivers to remove access to provocative stimuli (e.g. by installing parental locks on computers to prevent excessive use of pornography or removing credit card and financial account access from patients who are engaging in frequent buying sprees).(29) The multidisciplinary structure of our clinic helps ensure that all clinicians working with the patient and their carers are aware of problems related to ICDs and able to provide a consistent message.

Psychosis and manic syndromes in PD patients

Multidisciplinary treatment is also beneficial in addressing psychotic and manic symptoms in patients with PD. Psychotic symptoms in PD are associated with worse quality of life, increased caregiver burden and earlier nursing home placement.(4, 32, 33) Fourteen percent of non-demented PD patients experience hallucinations (often visual) or delusions, while an additional 12% experience “minor psychotic phenomena” such as illusions, the sense of a nearby presence or “passage hallucinations” (transient visual hallucinations seen only in the periphery).(34) These “minor” phenomena are important for clinicians to be aware of, though depending on a particular patient's level of distress or impairment associated with these phenomena, they usually do not require specific pharmacologic treatment. Although drug induced psychosis is commonly described (attributed both to dopaminergic and anticholinergic medications),(35-37) most cross-sectional studies of psychosis have failed to show an association with the presence or dosages of these medications.(4) However, in practice most providers decrease these medications when psychotic symptoms emerge, starting with those least likely to impact motor function, such as anticholinergics, amantadine, monoamine oxidase inhibitors, and then if symptoms persist, dopamine agonists and catechol-o-methyl transferase inhibitors. In severe cases, even the levodopa dose may need to be reduced. Additional studies are needed to reconcile the current trends in clinical practice with the reports of no association between dopaminergic medications and psychosis in cross-sectional studies.(34).

Hypomanic and manic syndromes also frequently emerge during treatment with dopaminergic medications. As many as 17% of patients with PD treated with dopaminergic therapy develop mania or hypomania, seemingly in association with starting or increasing these medications.(38) Higher doses of levodopa and being prescribed a dopamine agonist were both associated with increased risk of developing manic symptoms. Mania has been reported as a complication of DBS in approximately 4% of patients.(39) In Mr. W's case, adjusting the settings on the DBS to the minimum necessary to make the patient's motor symptoms tolerable, while aggressively treating the manic symptoms was ultimately successful. While psychotic and manic symptoms can emerge due to treatments for motor symptoms they may also reflect pre-existing psychiatric illness or be a direct consequence of PD itself. Close multidisciplinary collaboration can therefore be valuable in determining the etiology of neuropsychiatric symptoms. Regular meetings among the treatment team along with input from the patient and their family can also be helpful in prioritizing problems that need addressing.

The treatment of psychosis and acute mania is difficult because PD patients are predisposed to the adverse motor effects of antipsychotic dopamine receptor blockade. For this reason, the use of most antipsychotics is contraindicated in PD patients.(40) Exceptions include low dose quetiapine and clozapine, as well as pimavanserin, a 5HT2a inverse agonist with no activity at dopamine receptors that was recently approved for the treatment of psychosis in PD patients.(41) In addition, PD patients are also sensitive to side effects from some non-antipsychotic mood stabilizers (see table 1). For example, lithium causes a postural and action tremor, which can be difficult for PD patients to tolerate when combined with rest tremor,(42) and chronic valproate use has been linked to reversible Parkinsonianism.(43)

Treatment considerations

There are a number of scenarios where complicated interactions occur between a patient's motor symptoms, treatments for those symptoms, and neuropsychiatric conditions. Motor symptoms including off periods and drug-induced dyskinesias can effect mood and anxiety. Mood and anxiety in turn can each effect motor function. For example, people suffering from anxiety experience more freezing of gait.(44) Impaired cognition is common in PD and cognitive decline can make individuals with PD more vulnerable to developing affective illness, behavioral disturbances, and psychosis.(45) DBS can improve psychiatric symptoms in some patients. It can do so directly through stimulation of subcortical structures, as well as indirectly, by reducing the amount of dopaminergic drug therapy needed.(46) However, there is also evidence (strongest for stimulation of the subthalamic nucleus) that DBS can cause decreased verbal fluency.(47) In each of these scenarios, optimal treatment takes into account all of the distinct problems attributable to PD and benefits from multidisciplinary collaboration. An approach to providing clinical care that includes regular multidisciplinary meetings to discuss individual cases, regular input from the patient and carers to help determine treatment priorities and the possibility of continued multidisciplinary collaboration across levels of care (e.g. outpatient and inpatient) can be invaluable in managing such complicated problems.

Other considerations for managing the neuropsychiatric consequences of PD motor treatments include:

1. For depressive and anxiety disorders it is important to clarify the relationship between motor symptoms and neuropsychiatric symptoms. A journal documenting anxiety attacks in relation to medication schedule, including any skipped or delayed doses and any extra doses can be helpful in establishing whether there is such a relationship. When there is an association with motor fluctuations, medication adjustment or neurosurgical interventions to smooth out fluctuations can be effective. CBT techniques focused on helping patients tolerate fluctuations can also be effective. Treatment with antidepressant medication and supportive psychotherapy are also effective at treating depressive and anxiety disorders in PD patients. It is not known whether treatment with antidepressants increases the probability of developing an ICD in patients who are concurrently receiving dopaminergic therapy.

2. Patients who are overusing dopaminergic medications may benefit from treatment approaches that are used for other addictive disorders. As with other addictive behavior, it can be difficult for individuals to recognize the adverse consequences resulting from the behavior. Therefore, motivational interviewing (a technique for helping individuals resolve ambivalence regarding their desire to change a habitual behavior) can play an important role in helping patients recognize how their overuse of dopaminergic medications may be linked to problems in their lives or putting them at risk of adverse consequences. Addressing dysphoric emotions that may

drive compulsive use and limiting access to overused medications can also be important.

3. Especially in patients who are being treated with dopamine agonists, it is important to screen for ICDs. The first step in managing ICDs is to minimize or eliminate the use of offending medications. However, behavioral interventions may also be necessary. In patients who present with ICDs it is important to screen closely for other symptoms that may be part of a manic syndrome and provide anti-manic treatments if indicated.

4. Treatment options for psychosis and mania are limited in PD. Most antipsychotics are contraindicated in PD patients. Exceptions include low dose quetiapine and clozapine, as well as the 5HT2a receptor antagonist pimavanserin.

PD as a disease model for neuropsychiatric symptoms

In many ways, PD is an ideal disease model for investigating the pathophysiology of neuropsychiatric syndromes. PD has an increased prevalence of nearly every major type of neuropsychiatric syndrome and many have unique presentations associated with various aspects of PD or its treatments. The neurodegenerative process that causes PD is fairly uniform and is likely to affect brain structures in a predictable manner from the brainstem to the cortex.(48) PD may therefore be a particularly useful disease model for establishing associations between neuropsychiatric symptoms and specific neuropathology. Neuropsychiatric symptoms that are associated with dopaminergic medications (e.g. psychosis, ICDs) or complications of dopaminergic therapy (e.g. on-off fluctuations, dyskinesias) offer a similar advantage to investigators in that there is the ability to observe and in some cases manipulate a dose-response relationship between a centrally acting monoamine and neuropsychiatric symptoms. Ongoing research examining the relationship between on-off dopamine medication fluctuations and anxiety in PD, may lead to improved treatment of fluctuation-associated anxiety in PD and a better understanding of the pathophysiology of anxiety disorders in general. Finally, PD showcases the potential of functional neurosurgery, as DBS is one of the most effective and best established brain stimulation therapies and is actively being explored for the management of several neuropsychiatric disorders. Research on neuropsychiatric symptoms in PD is likely to lead not only to improved outcomes for patients with PD, but may improve knowledge of the mechanisms of neuropsychiatric symptoms in general.

Conclusions

Neuropsychiatric problems including depression, anxiety, overuse of prescribed dopaminergic medications, ICDs, psychosis and mania have a significant impact on the quality of life and overall morbidity in patients with PD. Mr. W's case illustrates the difficulty that can arise when trying to distinguish between primary psychiatric syndromes, manifestations of PD itself or complications of its treatment. Determining which of these factors are in play in a particular case has important implications for prognosis and management. Therefore, optimal management of neuropsychiatric symptoms in PD requires

close collaboration across disciplines to manage the many interactions among the pathophysiologic process that gives rise to PD, the motor symptoms, and the dopaminergic medications used for symptomatic treatment.

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References

1. Soh S, Morris ME, McGinley JL. Determinants of health-related quality of life in Parkinson's disease: a systematic review. Parkinsonism Relat Disord. 2011; 17:1–9. [PubMed: 20833572]
2. Shulman LM. Understanding disability in Parkinson's disease. Movement disorders. 2010; 25:S131–S135. [PubMed: 20187231]
3. Barone P, Antonini A, Colosimo C, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Movement Disorders. 2009; 24:1641–1649. [PubMed: 19514014]
4. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. Neurobiol Dis. 2012; 46:581–589. [PubMed: 22245219]
5. Stewart DA. NICE guideline for Parkinson's disease. Age and Aging. 2007; 36:240–242.
6. van der, Marck; Marjolein, A.; Bloem, BR. How to organize multispecialty care for patients with Parkinson's disease. Parkinsonism Relat Disord. 2014; 20:S167–S173. [PubMed: 24262173]
7. van der Eijk M, Nijhuis FA, Faber MJ, Bloem BR. Moving from physician centered care towards patient-centered care for Parkinson's disease patients. Parkinsonism Relat Disord. 2013; 19:923–927. [PubMed: 23742970]
8. van der Marck M, Munneke M, Mulleners W, et al. Integrated multidisciplinary care in Parkinson's disease:a nonrandomised, controlled trial (IMPACT). Lancet Neurol. 2013; 12:947–56. [PubMed: 23988337]
9. Mimura, Masaru, Oeda, Kawamura. Impaired decision-making in Parkinson's disease. Parkinsonism Relat Disord. 2006; 12:169–175. [PubMed: 16563850]
10. National Parkinson Foundation. [Accessed 8/12/16] Allied Team Training for Parkinson's. http://www.parkinson.org/expert-care-research/professional-training/allied-team-training-parkinsons
11. Duncan GW, Khoo TK, Yarnall AJ, et al. Health-related quality of life in early Parkinson's disease: The impact of nonmotor symptoms. Movement disorders. 2014; 29:195–202. [PubMed: 24123307]
12. Reijnders JS, Ehrt U, Weber WE, et al. A systematic review of prevalence studies of depression in Parkinson's disease. Movement Disorders. 2008; 23:183–189. [PubMed: 17987654]
13. Broen MP, Narayen NE, Kuijf ML, et al. Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis. Movement Disorders. 2016
14. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Movement Disorders. 2009; 24:1333–1338. [PubMed: 19425086]
15. Starkstein SE, Dragovic M, Dujardin K, et al. Anxiety has specific syndromal profiles in Parkinson disease: a data-driven approach. The American Journal of Geriatric Psychiatry. 2014; 22:1410–1417. [PubMed: 24200594]
16. Rutten S, Ghielen I, Vriend C, et al. Anxiety in Parkinson's disease: Symptom dimensions and overlap with depression and autonomic failure. Parkinsonism Relat Disord. 2015; 21:189–193. [PubMed: 25557888]

17. Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics. 2000; 41:15–23. [PubMed: 10665264]
18. Witjas T, Kaphan E, Azulay JP, Blin O, Ceccaldi M, Pouget J, Poncet M, Cherif AA. Nonmotor fluctuations in Parkinson's disease:Frequent and disabling. Neurology. 2002 Aug 13; 59(3):408–413. [PubMed: 12177375]
19. Leentjens A, Dujardin K, Marsh L, et al. Anxiety and motor fluctuations in Parkinson's disease: a cross-sectional observational study. Parkinsonism Relat Disord. 2012; 18:1084–1088. [PubMed: 22771284]
20. Maricle RA, Nutt JG, Valentine RJ. Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: A double-blind, placebo-controlled study. Neurology. 1995; 45:1757–1760. [PubMed: 7675241]
21. Fox SH, Katzenschlager R, Lim SY, Ravina B, et al. The movement disorder society evidence-based medicine review update: Treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2011; (3):S2–41. [PubMed: 22021173]
22. Romana PF, Colosimo C, Vanacore N, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. Movement disorders. 2005; 20:77–81. [PubMed: 15390130]
23. Cilia R, Siri C, Canesi M, et al. Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological characterisation to management and long-term outcome. J Neurol Neurosurg Psychiatry. 2014; 85:311–318. [PubMed: 23591553]
23. Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. J Neurol Neurosurg Psychiatry. 2000; 68:423–428. [PubMed: 10727476]
24. O'Sullivan SS, Evans AH, Lees AJ. Dopamine Dysregulation Syndrome. CNS drugs. 2009; 23:157–170. [PubMed: 19173374]
25. Okai D, Samuel M, Askey-Jones S, et al. Impulse control disorders and dopamine dysregulation in Parkinson's disease: a broader conceptual framework. European Journal of Neurology. 2011; 18:1379–1383. [PubMed: 21615625]
26. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. Arch Neurol. 2007; 64:1089–1096. [PubMed: 17698698]
27. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010; 67:589–595. [PubMed: 20457959]
28. Weiss HD, Pontone GM. Dopamine receptor agonist drugs and impulse control disorders. JAMA internal medicine. 2014; 174:1935–1937. [PubMed: 25329734]
29. Weiss HD, Hirsch ES, Williams JR, et al. Detection of impulse control disorders in Parkinson disease patients. The neurologist. 2010; 16:406–407. [PubMed: 21150395]
30. Ambermoon P, Carter A, Hall WD, et al. Impulse control disorders in patients with Parkinson's disease receiving dopamine replacement therapy: evidence and implications for the addictions field. Addiction. 2011; 106:283–293. [PubMed: 21134016]
31. Okai D, Askey-Jones S, Samuel M, et al. Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers. Neurology. 2013; 80:792–799. [PubMed: 23325911]
32. Aarsland D, Larsen JP, Tandberg E, et al. Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study. J Am Geriatr Soc. 2000; 48:938–942. [PubMed: 10968298]
33. Schrag A, Hovris A, Morley D, et al. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord. 2006; 12:35–41. [PubMed: 16271496]
34. Mack J, Rabins P, Anderson K, et al. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. The American Journal of Geriatric Psychiatry. 2012; 20:123–132. [PubMed: 21617521]
35. Celesia GG, Barr AN. Psychosis and other psychiatric manifestations of levodopa therapy. Arch Neurol. 1970; 23:193–200. [PubMed: 5456717]
36. Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Movement Disorders. 2000; 15:201–211. [PubMed: 10752567]

37. Chou KL, Messing S, Oakes D, et al. Drug-induced psychosis in Parkinson disease: phenomenology and correlations among psychosis rating instruments. Clin Neuropharmacol. 2005; 28:215–219. [PubMed: 16239760]
38. Maier F, Merkl J, Ellereit AL, et al. Hypomania and mania related to dopamine replacement therapy in Parkinson's disease. Parkinsonism Relat Disord. 2014; 20:421–427. [PubMed: 24467817]
39. Temel Y, Kessels A, Tan S, et al. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: a systematic review. Parkinsonism Relat Disord. 2006; 12:265–272. [PubMed: 16621661]
40. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Movement Disorders. 2011; 26:S42–S80. [PubMed: 22021174]
41. Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin2A receptor inverse agonist, for the treatment of Parkinson's disease psychosis. Neuropsychopharmacology. 2010; 35:881–892. [PubMed: 19907417]
42. Baek JH, Kinrys G, Nierenberg AA. Lithium tremor revisited: pathophysiology and treatment. Acta Psychiatr Scand. 2014; 129:17–23. [PubMed: 23834617]
43. Zadikoff C, Munhoz RP, Asante AN, et al. Movement disorders in patients taking anticonvulsants. J Neurol Neurosurg Psychiatry. 2007; 78:147–151. [PubMed: 17012337]
44. Lieberman A. Are freezing of gait (FOG) and panic related? J Neurol Sci. 2006; 248:219–222. [PubMed: 16797596]
45. Giladi N, Treves T, Paleacu D, et al. Risk factors for dementia, depression and psychosis in long-standing Parkinson's disease. J Neural Transm. 2000; 107:59–71. [PubMed: 10809404]
46. Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. The Lancet Neurology. 2012; 11:429–442. [PubMed: 22516078]
47. Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann Neurol. 2009; 65:586–595. [PubMed: 19288469]
48. Braak H, Ghebremedhin E, Rub U, et al. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318:121–134. [PubMed: 15338272]

Clinical Case Scenario: A 65-year-old man with neuropsychiatric complications from treatments for Parkinson's disease

Mr. W was a 65-year-old married, male with Parkinson's disease (PD) who presented to a movement disorders clinic with a chief complaint that his “throat was closing off” during motor off-periods. Prior to his PD diagnosis, Mr. W was generally healthy, enjoyed stable relationships and earned a professional degree that enabled him to have a successful and lucrative career. Beginning in his 30s he had several depressive episodes treated with brief courses of psychotherapy and medication. At age 57, he experienced severe depressive symptoms that were largely refractory to several antidepressant trials over the course of one year. Ultimately his mood did improve, though he still felt physically slowed and had developed a resting tremor in his left hand. At age 58 he was diagnosed with PD and started on carbidopa/levodopa with clear improvement in his movement symptoms.

By age 64, Mr. W began to notice that his levodopa was wearing off before his next scheduled dose causing his motor symptoms to fluctuate. During his off periods, he complained of worsening bradykinesia, gait difficulty, cognitive slowing, and voice changes. The decline in work performance related to these symptoms led Mr. W to retire. His off-periods became associated with intense anxiety, and the sensation that his “airway was closing.” He began taking additional carbidopa/levodopa in an attempt to prevent off-periods and scheduled a consultation at a specialized movement disorders clinic. During the drive to this clinic from another state, the patient and his wife stopped at two hospitals seeking emergency services because of his fear that his “throat was closing off.” Medical workup was unremarkable.

When Mr. W was seen in the movement disorders clinic, he was found to have akathisia with severe dyskinesias. He was admitted to the neurology service and a psychiatric consultation was obtained. It was determined that he was experiencing severe anxiety attacks that were closely associated with off-periods during motor fluctuations. His levodopa was decreased and pramipexole was added in an effort to minimize fluctuations. He improved motorically while in the hospital. However, the severe episodic anxiety (which were often full fledged panic attacks) restarted shortly after discharge.

He returned to the clinic and was re-admitted to the neurology service. He was transferred to a specialized multidisciplinary inpatient bed reserved for patients with neuropsychiatric complications of PD after his treatment team learned that he was leaving the hospital to visit erotic establishments and having other behavioral disturbances. His wife revealed that, at home, he was taking substantially more levodopa and pramipexole than prescribed. Mr. W acknowledged feeling that the medication not only made it easier for him to move, but also improved his sense of wellbeing. In addition, he was now experiencing frequent mood changes, vacillating between elation and irritability. For several weeks, he had been sleeping less than two hours per night and was engaging in uncharacteristic hypersexual behavior. He had also started trading stocks online and was making plans to buy and sell houses. His exam was notable for rapid, pressured speech with flight of ideas.

Mr. W was diagnosed with bipolar disorder, type I, manic with a comorbid dopamine dysregulation syndrome. Dopaminergic medication was thought to be contributing to the initiation and worsening of his manic state. Pramipexole was tapered and discontinued. However, the patient remained manic requiring hospitalization for over two months. Ultimately, his mania resolved on valproate and quetiapine. On discharge, Mr. W's motor symptoms were objectively worse. He followed up in a multidisciplinary clinic for PD patients where a nurse specialist helped coordinate care and his case was reviewed in consultation by a movement disorders neurologist, a functional neurosurgeon, a neuropsychiatrist and a neuropsychologist. This team met regularly to discuss his (and others') cases in order to provide coordinated follow up for his symptoms. Considering his continued disability from motor fluctuations exacerbated by his need to stop the dopamine agonist, this team recommended that he undergo bilateral subthalamic nucleus deep brain stimulation (DBS) surgery.

When Mr. W's DBS was activated, it quickly led to improved motor symptoms, eliminated end of dose wearing off, and allowed him to remain at lower doses of dopaminergic medications. However, when his stimulation voltage was increased, he again developed manic symptoms, despite being maintained on valproate and quetiapine. During this episode he complained of fully formed visual hallucinations of “cat-headed people.” He was re-hospitalized on the multidisciplinary PD unit where his DBS settings were reduced to their previous level and lithium was added. Mr. W remained hospitalized for six weeks before ultimately returning to a euthymic state. More than a year after this last hospitalization, his motor symptoms are well controlled and his mood remains stable on quetiapine, valproate and lithium.

Table 1
Antipsychotic and mood stabilizing medications for use in patients with PD

Antipsychotic medications	**Starting dose**	**Titration**	**Max dose**	**Side effects/special considerations**
Quetiapine	12.5-25 mg HS	Increase by 25mg every few days as tolerated	250 mg	Monitor for orthostatic hypotention
Clozapine	12.5-25mg HS	Increase by 25mg every few days as tolerated	Once level greater than 300, unlikely to get further clinical benefit with increased dose	Monitor for orthostatic hypotentension; 1% per year risk of agranulocytosis, requires regular blood monitoring
Pimavanserin	34mg per day	None	34mg per day	FDA approved in 2016 for treating psychosis in PD
Other antipsychotic medications*				**Contraindicated.** Monitor carefully for worsening Parkinsonianism / neuroleptic-malignant syndrome if exposed
Mood stabilizing medications**				
Lithium	150mg HS	Increase in 150-300 mg increments as tolerated	Blood level of 0.8-1.2 for treatment of mania	Commonly causes tremor which may be particularly hard for PD patients to tolerate
Valproate	250 mg HS	Increase in increments of 250-500mg as tolerated	Blood level of 85-125 for treatment of mania	May worsen Parkinsonian symptoms. May increase ammonia which can contribute to delirium

* Movement Disorder Society practice guidelines advice against the use of other neuroleptics due to concern for safety in PD

** Use of other anti-epileptic mood stablizers do not generally necessitate special precautions when used in PD