Recognizing and Treating Neuropsychiatric Symptoms in Parkinson's Disease

Kathryn A. Chung, MD

From the Department of Neurology, Oregon Health & Science University, Portland, OR.

ABSTRACT
- **Objective:** To review the clinical characteristics, epidemiology, and management of the most common neuropsychiatric symptoms (NPS) in Parkinson’s disease (PD).
- **Methods:** Literature review.
- **Results:** PD has traditionally been considered a disease of impaired motor function. However, neuropsychiatric complications, such as fatigue, depression, anxiety, psychosis, impulse control disorders, and apathy, frequently complicate the course of the illness. Although the development of new medication options in recent years has had a positive benefit on the management of these troublesome symptoms, responses are frequently suboptimal. The development of valid instruments to measure neuropsychiatric symptoms has been vital in research efforts to bridge the gaps in our understanding. Further elucidation of neuropsychiatric pathophysiologies will help to define treatment targets and has the potential to expand our therapeutic armamentarium.
- **Conclusion:** While NPS affect patients with established disease, recent investigations have demonstrated risk of symptoms in those with early untreated stages of PD; therefore, better understanding of NPS should be the goal of practitioners treating the entire continuum of PD. This review will focus on the clinical characteristics, epidemiology, and management of the most common neuropsychiatric symptoms in PD.

Impulse Control Disorders
The recognition that dopaminergic drugs were successful at treating many symptoms of PD was followed by the disturbing realization that impulse control disorders could be an unfortunate side effect in a substantial minority. Impulse control disorders as defined by DSM-IV [1] are disinhibited behaviors that are maladaptive and recurrent, causing personal and relationship consequences. The impulse control disorders that became associated with PD and medication intake, particularly dopamine agonist use, included gambling, hobbyism, punding (stereotyped, seemingly purposeless behaviors), excessive sexual behavior, shopping, hoarding, and less commonly, compulsive eating. The prevalence estimates of these behavioral disturbances range from 6% to 15.5%, compared with < 2% in the general population [2,3]. The addiction-like dopamine dysregulation syndrome, whereby patients self-medicate with high doses of levodopa and short-acting dopamine agonists beyond what is needed for motor control, can lead to significant impairment of the therapeutic alliance in addition to other patient personal relations. With the advent of surgical options to treat PD and its medication complications, it was observed that stimulation of the subthalamic nucleus could be associated with the spectrum of impulse control disorders [4].

Epidemiology/Risk Factors
In a recent systematic review of the literature of impulse control disorders in PD [5], the authors determined that...
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dopaminergic therapy caused compulsive or impulsive behaviors in approximately 10% of PD patients in the course of their treatment, with pathologic gambling and hypersexuality most frequently experienced. Multiple impulse control disorders are not uncommon and may coexist in one-quarter of patients with compulsivity. There appeared to be more disordered behavior with higher comparable doses of agonists. The authors concluded that impulse control disorder symptoms tended to occur with initiation or dose increases of direct D_{2}/D_{3} agonists, such as pramipexole and ropinirole. Importantly, impulse control disorder behavior improved if not resolved with discontinuation or reduction of dosage of the agonist, even if a compensatory levodopa dosage is added or increased. Perhaps not surprisingly, it was observed that if patients had a preexisting impulse control disorder prior to PD or the initiation of treatment, there was a high likelihood of worsening of symptoms. This small subgroup is estimated at about 1% of PD subjects, which corresponds to the prevalence of impulse control disorders in the general population. Other identified potential risk factors for impulse control disorder development include male gender, young age at onset, a personal or family history of addiction, novelty or risk seeking personality, and a concurrent diagnosis of depression [3]. In a recent study of early PD patients, the risk of developing an impulse control disorder became important once treatment with dopaminergic drugs began and continued for a year or more [6].

**Pathogenesis**

The pathogenesis is not fully understood, however, mesolimbic dopamine alterations are strongly suspected. It has been long speculated that the high doses of dopamine needed to replete the relatively depleted dorsal striatum overdose the “intact” ventral striatum and cause this neuropsychiatric disorder [7–9]. The additional cognitive impairments in PD, which can include problems with attention, working memory, planning, forethought and decision-making, are faculties that can markedly increase susceptibility to impulse control disorder [8].

The role of serotonin deficiency in the PD brain and its part in inhibiting the patient’s ability to delay rewards adds to the complexity of impulse control disorder pathogenesis. Dorsal raphe nuclei disease in PD results in loss of serotonin innervation to substantial portions of the prefrontal and motor cortices in addition to basal ganglia substructures like the striatum, pallidum and subthalamic nucleus [10]. Together with dopamine, serotonin may work to regulate risk-sensitive decision making, response inhibition, waiting for future rewards, and overall impulse control. Its relative loss therefore also likely contributes to tipping the balance towards impulse dyscontrol [11,12]. The role of other neurotransmitters such as opiate systems involved in the process of acquisition and maintenance of addictive behaviors like dopamine dysregulation syndrome remains to be fully understood.

**Treatment**

The most successful strategy to address this problem is to reduce or eliminate the offending medication, usually the dopamine agonist. This may be associated with worsening apathy, anxiety or depression; however, substituting levodopa can be a successful strategy in many cases [13]. Zonisamide was described to be possibly effective in a trial of 15 subjects; however, the open label nature of this evidence must be considered as with other case reports using valproate, donepezil, and selective serotonin reuptake inhibitors (SSRIs) [14–16].

**Fatigue**

An easy to understand operational definition of fatigue is that it is a state of extreme tiredness, weakness, or exhaustion, either physical or mental or both. Fatigue is not uncommon in the general population [17] but is increasingly recognized to occur in numerous disease conditions and is frequently encountered in PD and multiple sclerosis. The latter is of special significance in the consideration of the neurotransmission of fatigue, as it is not thought to be a disease of dopamine deficiency. The pathophysiology remains unclear, and it may differ depending on whether the fatigue is experienced as more physical or mental, or rather motor versus nonmotor as some authors propose.

Fatigue has been conceptualized as central or peripheral in character. Peripheral fatigue is best understood as muscular fatigue caused by repetitive muscular contraction or reduced force generation [18]. Central fatigue however, is divided into mental or physical fatigue. Mental fatigue can occur after sustained attentive or emotional activity. It may alternatively be provoked after boring repetitive tasks or lack of intellectually stimulating activity. Physical fatigue is the sense of body exhaustion or energy to perform physical tasks even though the ability to carry them out exists.
Epidemiology
As recognition of the problem of fatigue increased in the last 2 decades, the realization that one-third to one-half of patients experience it at some point has improved opportunities for recognition and treatment [19]. Fatigue may be the presenting symptom in one-third of patients prior to actual motor symptom onset [20]. Half of untreated PD patients in a biomarker cohort study reported fatigue [6]. Unfortunately, it is also described by patients as one of the most disabling symptoms, causing significant impact on quality of life [19]. Fatigue in PD is associated with higher rates of depressive symptoms, but occurs with higher prevalence in nondepressed patients [21]. Poor ability to initiate and sustain activity due to fatigue is different from depression, excessive sleepiness, or impaired motor function [22,23].

Pathophysiology
The pathophysiology of fatigue remains somewhat unclear, though physical fatigue is likely a significant part of the problem and related to dopamine deficiency based on studies of time and force generation of keyboard strikes in PD subjects before and after L-dopa administration. These subjects had declines in force and increased physical fatigue which improved after L-dopa [24]. In other studies using transcranial magnetic stimulation to study changes in cortical excitability, the degree of physical fatigue correlated with abnormalities in motor evoked potentials during fatiguing exercising. These studies also support the hypothesis that fatigue is a motor symptom [25,26]. In the ELLDOPA study, fatigue worsened more in PD subjects treated with placebo [27]. Other imaging studies have suggested suggested nondopaminergic mechanisms including serotonergic pathway abnormalities [28], thus the question behind the etiology and solution for all cases of fatigue remains to be settled.

Diagnosis
The diagnosis is fatigue may be challenging as it may mask as depression or apathy. There are a number of fatigue rating scales available; however, the validated Parkinson’s Fatigue Scale (PFS) supersedes many of the problems of using a generic scale which could overlap motor questions and potentially be confounding [29,30].

Treatment
Most important is awareness and vigilance for the symptoms of fatigue, depression, and apathy and effort to distinguish between them. It may require structured interviews or assessment tools to properly diagnose the problem. Treatment is less clear in that few studies have clearly indicated the best treatment options. In placebo-controlled trials, methylphenidate did improve fatigue as did levodopa [31]. Modafinil, a hypocretin modulator and a drug first approved by the FDA for treatment of narcolepsy, has demonstrated mixed results in recent years. It may reduce physical fatigue and reduce excessive daytime sleepiness but likely does not reduce subjective symptoms of fatigue [32]. L-dopa can significantly reduce fatigue in many patients, which would argue that it often is a motor symptom [33,24]. In a post-hoc analysis of the ADAGIO delayed start study, patients taking rasagiline 1 mg/day and 2 mg/day (the latter dose exceeds the usual clinical dosing) showed significantly less worsening of symptoms on the PFS compared to placebo over time [34]. It is important to realize that once motor symptoms are optimally treated with dopaminergic medications, while many patients will feel significant relief from fatigue some patients will continue to feel symptomatic.

Apathy
The definition of apathy has become more complicated and refined, incorporating findings from the study of brain disease and behavioral analysis. Marin’s classic elaboration of apathy as lack of motivation not attributable to diminished level of consciousness, cognitive impairment, or emotional distress has been built upon by Levy and Dubois [35–37]. They suggest apathy may be better thought of as an observable behavioral syndrome characterized by a quantitative reduction of self-generated voluntary and purposeful behaviors. They suggest 3 apathetic subtypes: emotional, cognitive, and auto-activational, which reflect different disease states accounting for failure of normal goal-directed behavior.

Epidemiology
Prevalence estimates for apathy in PD vary. This is likely due to the varying recruitment criteria among studies, with some including patients with comorbid depression and dementia and others containing only “pure apathy.” Other reports may have had referral bias issues, as community-based studies report lower prevalences in general. In a group of newly diagnosed PD patients, using more restrictive criteria (apathy subscale of the neuropsychi-
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Apathy has been associated with longer disease duration, male gender [40], higher daily levodopa doses [41], more severe parkinsonism [38], and lower education status, though the latter feature remains under debate. Early cognitive deficits appear to be a risk factor for development of apathy [42]. The patterns of cognitive dysfunction and apathy remain unsettled in the literature.

Pathology

The pathology of atrophy remains unexplained and is unlikely to be reduced to a simple atrophy of one nucleus or the tone of one circuit. However, in a small neuroimaging study, severity of apathy correlated with atrophy of the bilateral nucleus accumbens [43], and it is notable that one major input to the nucleus accumbens is the amygdala. According to Braak staging, by stage 4 significant involvement of the amygdala by Lewy bodies has occurred. Others have found changes in grey matter density that could correlate with deficits of the prefrontal-basal ganglia circuitry to produce dysfunction of segregated frontal-subcortical loops. These may correlate with the “autoactivation” deficit pattern of apathy in which patients have a lack of self-initiated actions, even thoughts, though appear more normal when given externally prompted responses [37,44].

Assessment

Clinically, the relationship between apathy and depression can be hard to disentangle, especially since many studies have found an association between them, especially with regards to apathy and anhedonia. Depression may feature negative self-thoughts and sadness while apathy is notable for lack of initiation and effort. Viewed over a longer period of time, apathy tended to worsen in a linear fashion, where depression tended to fluctuate with improvements and exacerbations.

The Movement Disorders Society task force has recommended the Lille Apathy Rating Scale (LARS) for assessment of apathy; English and French versions have been validated in PD patients. It uses a semi-structured interview format assessing 4 dimensions of apathy: self awareness, intellectual curiosity, emotion, and action initiation [45–47].

The impact of apathy cannot be underestimated as this poor show of motivation or effort leads to lack of engagement in old activities or interest in new ones. Spouses may misinterpret this change in behavior as laziness or deliberate social withdrawal, or perhaps entitlement. It is not surprising that apathy routinely shows up on quality of life (QoL) questionnaires as highly impacting patients and families. In one study, apathy was the nonmotor symptom most likely to cause caregiver distress in PD [40,48–50].

Treatment

No approved drugs exist for treatment of apathy. However, clinical experience often confirms that dopaminergic modulation can be helpful in the treatment of apathy as indirect evidence suggests. A meta-analysis of controlled trials using pramipexole and Part I of the Unified Parkinson’s disease rating scale (UPDRS) (secondary measure) showed the medication improved scores on this measure of motivation and mood in non-depressed subjects [51] with PD. Rare patients undergoing subthalamic deep brain stimulation have been reported to experience new and sometimes severe apathy after surgery [52]. This was posited at least in part to be the result of reduction of dopaminergic medication due to surgery.

Nondopaminergic pharmacotherapy of apathy is in its infancy. A recent controlled trial of rivastigmine in 31 French subjects with moderate to severe apathy based on LARS showed that 6 months of treatment at 9.5 mg/day improved average scores from –11.5 to –20 compared with placebo. While quality of life did not improve, caregiver burden did. The investigators found in this group of subjects that apathy was a possible herald for early dementia in PD [53].

A post-hoc analysis of the ADAGIO study (rasagiline or placebo in PD patients taking antidepressants) found that rasagiline use was associated with a nonsignificant slowing of apathy development during the trial [54].

Psychosis

Psychotic symptoms are a common occurrence in drug-treated patients, with visual hallucinations occurring in up to 30%, though over a 20-year period up to three-quarters of patients may develop visual hallucinations. After visual, the most common type of hallucination is auditory, followed by the other affected senses such as tactile, olfactory, or even taste [57]. Delusions, which tend to be paranoid in nature, occur in about 5% of
The presence of psychotic symptoms is associated with poorer quality of life [58].

Symptomatology
The visual hallucinations of PD are usually quite stereotyped, and have been described as “minor” and “non-minor” [59]. Minor hallucinations refer to transient peripheral field stimuli that disappear when brought into central focus, “something flashed by,” a sense of a living being nearby, “a presence in the room,” or illusions whereby objects are transformed, e.g., a bush in the yard is a deer.

Auditory hallucinations tend to be vague or indistinct sounds, like music in another room as opposed to voices speaking directly to the patient as might be experienced in a primary psychotic disorder. Tactile forms often involve insects or other animals crawling on the skin. Olfactory hallucinations may take the form of smelling perfume, toxic odors from room vents, etc.

Early in the experience, the visual hallucinations may be amusing in that they consistently remain nonthreatening, similar day to day, and sometimes oddly provide an aspect of comfort or companionship to the patient. More commonly, the hallucinations are bothersome to the patient because the experience indicates to the patient that there is something wrong with their mind. Visual hallucinations often begin in low-stimulus environments, often in the evening or other low-light conditions, but as the problem advances they can occur at any time of day. While visual hallucinations may initially occur for only seconds at a time many days apart, the frequency and duration can increase until they occur hours at a time every day and are accompanied by multiple other visual hallucinations, delusions, and confusion [60].

Delusions tend to be more distressing to patients and caregivers because they are often paranoid in nature. The patient is more likely to act out due to the anxiety the paranoia creates. For example, she may change passwords to online accounts due to a belief that unknown assailants are after her finances. He may go to great lengths trying to prove his wife is cheating.

Risk Factors
While the primary risk factor for psychotic symptom development is dementia [57], it occurs in nondemented patients. Other associations include reduced visual acuity [56], visual processing impairment [61–65], use of dopamine agonists, REM behavior disorder, duration of PD, axial rigidity subtype of disease [61,66–68]. The pathophysiology of psychosis in PD is likely complex and remains currently unexplained. The role of excess dopamine has been described above, but there is also data suggesting cholinergic deficits in the cortex may also contribute. Excess serotonin (increased 5HT2A receptor subtypes) in the temporal lobe within the visual processing pathway has been postulated to be of significance [69,70]. Hypometabolism in visual association areas of the brain in subjects with visual hallucinations has been demonstrated in PET and functional MRI studies [64,71]. This is similar to findings in patients with dementia with Lewy bodies [72].

This review focuses on the primary forms of PD-related psychosis, which occur with a clear sensorium and generally longer exposure to dopaminergic medication. It is important to distinguish 2 other common scenarios in which hallucinations or delusions may occur. In the common toxic-metabolic delirium, a clouded sensorium with attention deficits may be the only clue to the etiology of new onset confusion with visual hallucinations. It is highly likely that resolution of the underlying medical problem will lead to resolution of the new onset psychosis and encephalopathy. In a second scenario, hallucinations precede or occur very shortly after the onset of initiation of dopaminergic medication. This differs from the classic syndrome described earlier, in particular when visual hallucinations precede any initiation of medication, and likely represents the distinction between a diagnosis of Lewy body disease and PD [60].

Treatment
Management of psychosis is approachable, but often the outcome is unsatisfactory and associated with trade-offs in motor control. It is unfortunately true that psychotic symptoms are often associated with increased caregiver burden and are a cause of increased nursing home placements [73]. When considering the workup of psychotic symptoms, the differential diagnosis includes delirium, dream enactment (REM behavior disorder), or less commonly, Bonnet syndrome.

A delirium may be precipitated by a difficult to diagnose infection; new-onset confusion and psychotic symptoms may be the heralding presentation. Urinary tract or upper respiratory tract are common vulnerable sources of infection. Once infection is ruled out, the next practical step is to review the patient’s medication list and manage centrally acting drugs that could be contributing to the altered sensorium. A recent prescription of opioids for a
dental treatment or a new muscle relaxant may be a cul-
prit, though it is not that usual. A bladder anticholinergic
could be suspect and is worth eliminating especially if its
addition coincided with the appearance of the psychotic
symptoms. Once the non-dopaminergic medications
have been reduced/eliminated, then the PD medications
should be considered. The general approach is to elimi-
nate the medications that provide the least benefit while
being more likely to contribute to psychotic symptoms.
Anticholinergic medications, dopamine agonists, selegi-
line should all be uppermost in that consideration until
one is left with L-dopa and COMT inhibitors (the latter
function to increase levodopa availability). Then COMT
inhibitors and levodopa can be reduced; however, at any
point motor control can suffer with the loss of symptom-
atic therapies [74].

Clozapine is effective against psychotic symptoms in
PD, at doses much lower than used in schizophrenia
(300–600mg/day). The average dose in the US random-
ized controlled clinical trial was 25 mg/day, with no as-
associated motor worsening. Patients in the United States
are required by the FDA to be placed in a computer-
based registry and monitored for agranulocytosis for the
duration of clozapine therapy. This rare adverse event is
not dose related. Orthostasis can occur at these low doses
however. Fortunately the metabolic syndrome is not as-
associated with this range of administration [75,76].

Quetiapine was not found to be effective in 3 blinded
randomized controlled trials despite its rather common
use for this purpose. It was not associated with motor
worsening, however.

Other neuroleptic medications have not resulted in
widespread use, because trials have been open label, or
outcomes demonstrated motor worsening. Cholinesterase
inhibitors have been the subject of a few positive case se-
ries, however results appear to be sporadic, the effect size is
relatively small, and side effects of this medication class are
common [77–79]. It is clear that there is an unmet need
for a medication for psychotic symptoms. Clozapine is ef-
fective but onerous in its monitoring requirements. Practi-
cally speaking, there are relatively few PD patients who
take advantage of it because of its feasibility challenges.
Yet the problem of psychotic symptoms is a significant one
that imposes important challenges to the patient and care-
giver, and may limit the number of medications that the
patient needs in order to optimize quality of life.

Pimavanserin, a novel medication which acts as a
selective serotonin inverse agonist, is in the early applica-
tion stages for FDA approval for treatment of psychotic
symptoms in PD [80]. In its pivotal phase III controlled
trial, the drug reduced not only positive symptoms
(hallucinations/delusions) without causing motoric wors-
ening, but also reduced caregiver burden. Pimavanserin
improved certain sleep features without causing daytime
sedation. If this drug meets final approval, it may present
an exciting option for many patients for whom treatment
was previously limited.

Depression
A study of early PD suggested that depression is often un-
recognized and frequently untreated [1]. Indeed it is not
usual for depression to predate the diagnosis of PD by
an average of 4 to 6 years [81]. Expanding to the larger PD
population, it is generally accepted that about 30% to 50%
of PD patients experience clinically significant depression,
and once diagnosed may have a long term course, or may
recur [82,83]. This is important as untreated depression is
an important cause of poor quality of life in early PD. In
addition depression can exacerbate motor disability, lead
to earlier motor treatment with medication, and increase
caregiver stress [83–85].

Diagnosis
Diagnosing depression in PD is more challenging as so-
matic, cognitive, and vegetative symptoms of altered mood
can be imitated features in PD, such as facial masking,
fatigue, sleep changes, weight loss, and working memory
dysfunction (Table). Therefore, nonsomatic features tend
to be more valuable to the clinician to query, such as the
hedonic state (does the patient seek pleasurable activ-
ity?), mood, pessimism, state of hope, sense of capabil-
dy?), mood, pessimism, state of hope, sense of capabil-
ity?[86,87]. Diagnosis of major and minor depression as
well as dysthymia in PD using DSM-IV criteria has been
validated [88]. To avoid underdiagnosis of this important
commonly coexisting comorbidity, being inclusive with
somatic overlapping features is still more important than
trying to distinguish which disease state it belongs to.

A number of clinimetric rating scales for depression
have been used and their advantages have been largely
related to their objective nature (quantifiable); thus, they
tend to be most useful in epidemiologic research studies
or for larger scale screening purposes. Examples include
the the Beck Depression Inventory, the Geriatric Depres-
sion Scale, and the Hamilton Depression Scale, all of
which have been shown to be valid tools in PD (with the
exception of the UPDRS Depression). It is important to
note that they do not substitute for a diagnostic clinical interview [89].

Suicide is not common in PD, however suicidal ideation is estimated at about 11% in PD patients [90], and while there was concern initially after deep brain stimulation procedures began that suicide incidence was increased, evidence does not support this [91].

Pathophysiology

The pathophysiology of depression in PD is largely unknown however is thought to be less causally due to psychosocial factors and more etiologically driven by brainstem monoamine and serotonergic dysfunction [92]. Nonetheless, similar to other chronic conditions, PD patients can certainly develop fear of disability, guilt about impact on others, or other reactive mood changes. Overall, rates of depression are higher in PD compared with patients with similar conditions matched for disability [93].

Treatment

First, the clinician must determine if depression is a result of short-term fluctuations, chronic undertreatment of motor disease, or longer-term mood phenomenon. One important pattern to recognize are mood fluctuations, which can parallel motor OFF-ON cycling. It can be valuable to distinguish this as “subsyndromic” depression or anxiety (sometimes referred to as “OFF dysphoria”), as it can respond to improvement in antiparkinsonian medication dosing patterns that reduce fluctuations[94–96]. Similarly, elevating chronic motor undertreatment to goal therapy can result in mood normalization.

If symptoms persist despite optimization of motor/nonmotor fluctuations or chronic undertreatment and are severe enough to warrant treatment, then therapies used can range from nonpharmacologic education, support, and mental health referrals, as well as pharmacologic support in the form of medications.

A frequent but uncontrolled observation was that when undertreatment of motor disease was finally redressed, mood often improved. A multicenter randomized controlled trial of pramipexole in PD patients without motor fluctuations but with mild to moderate depressive symptoms showed the drug improved scores on the Beck Depression Inventory over a 12-week period. The improvement in mood was 6 points overall, but by 2 points over placebo, illustrating the importance of the size of the placebo effect [97]. Given the potential side effect profile of dopamine agonists, it may be useful to weigh the antidepressant effects only when their motor benefits are already being employed.

Controlled trials have demonstrated efficacy of both selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI) antidepressants in PD. Clinical trials have demonstrated efficacy against placebo or with other antidepressant comparators. Examples of drugs with demonstrated efficacy include citalopram, paroxetine, venlafaxine, and nortriptyline. Results have attempted to illuminate the small unique differences between classes of antidepressants or dynamic properties between drugs within a class. For example, desipramine may nudge scores on a mood scale a few weeks sooner than a purer SSRI. Paroxetine (SSRI) versus venlafaxine (SNRI) improved mood scores comparably in a multicenter trial with a placebo comparator. In general, all have all been demonstrated to be effective and with a relatively low side-effect profile, comparable to the general population[98–102]. While case reports exist in the literature, the interaction of monoamine oxidase B inhibitors and SSRIs has not caused significant hypertensive crises or risk of serotonin syndrome [103,104]. Electroconvulsive therapy (ECT) can be used for severe refractory depression in PD as for non-PD patients, with case reports of very effective results. Due to the rarity of use, systematic evidence for its use is lacking [105,106].

Other novel agents and techniques such as omega-3 fatty acids [107] and repetitive transcranial magnetic stimulation [108] have been reported with promising early results. Cognitive behavioral therapy (CBT), which may involve stress management techniques, sleep hy-

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<th>Feature</th>
<th>Major Depression</th>
<th>Parkinson’s Disease</th>
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<td>Decreased energy</td>
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<td>Sleep changes</td>
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<td>Appetite/weight changes</td>
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<td>Cognitive changes (ie, poor memory/concentration, indecisiveness)</td>
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Table. Overlapping Clinical Features in Parkinson’s Disease and Depression
Neuropsychiatric symptoms are common in PD and new knowledge about clinical features, epidemiology, and treatment options has been gained in the last decade, though much remains to be discovered. The development of valid instruments to measure neuropsychiatric symptoms has been vital in these research efforts to bridge the gaps in our understanding. Further elucidation of the pathophysiology of neuropsychiatric symptoms will help to define treatment targets and likely fuel drug development and the discovery of drugs with more potent benefit and fewer side effects.

**Anxiety**

Anxiety is also common in PD, at least as common as depression considering that prevalence estimates suggest up to 50% of patients experience it [110–112]. Manifestations of anxiety may include panic attacks, generalized anxiety disorder, social anxiety, or other phobias [113]. Anxiety has an important negative impact on health-related quality of life and is often underrecognized by clinicians [114]. While reliable and valid scales to measure anxiety have been lacking in PD, a new effort has yielded the “Parkinson Anxiety Scale” though full clinimetric properties of the scale remain to be demonstrated (sensitivity to change) [115].

Anxiety that parallels the timing of motor OFF-ON cycling is important to recognize. This “subsyndromic” anxiety or anxiety disorder not otherwise specified (ie, the anxiety does not meet DSM-IV criteria) can respond to improvement in antiparkinsonian medication dosing patterns that reduce fluctuations [116,117]. Indeed, the presence of motor fluctuations is the principle marker of anxiety in many studies [118–120]. In an analogous manner, anxiety can predate PD by years and be part of the nonmotor amalgam of features heralding the disease [6,121].

**Treatment**

Systematic controlled trials of anxiolytic treatment for PD are lacking; therefore, SSRIs are prescribed for this purpose as in non-PD patients. Until SSRIs are demonstrated to be of benefit in anxiety, they are likely safer than use of benzodiazepines, which are associated with risk for falling, cognitive dysfunction, or autonomic dysregulation in PD patients when used during waking hours. Psychotherapy and other nonpharmacologic approaches are likely to be of benefit. A small study of neuromuscular (massage) therapy demonstrated improvement on the Beck Anxiety Inventory in PD [122]. A case report of ECT for severe anxiety has been published [123].

**Conclusion**

Neuropsychiatric symptoms are common in PD and new knowledge about clinical features, epidemiology, and treatment has been gained in the last decade, though much remains to be discovered. The development of valid instruments to measure neuropsychiatric symptoms has been vital in these research efforts to bridge the gaps in our understanding. Further elucidation of the pathophysiology of neuropsychiatric symptoms will help to define treatment targets and likely fuel drug development and the discovery of drugs with more potent benefit and fewer side effects.

**Corresponding author:** Kathryn A. Chung, MD, Department of Neurology, Oregon Health & Science University, Portland, OR, chungka@ohsu.edu.

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**References**

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