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The Neuropsychiatry of Parkinson Disease: A Perfect Storm

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Abstract

Affective disorders, cognitive decline, and psychosis have long been recognized as common in Parkinson disease (PD), and other psychiatric disorders include impulse control disorders, anxiety symptoms, disorders of sleep and wakefulness, and apathy. Psychiatric aspects of PD are associated with numerous adverse outcomes, yet in spite of this and their frequent occurrence, there is incomplete understanding of epidemiology, presentation, risk factors, neural substrate, and management strategies. Psychiatric features are typically multimorbid, and there is great intra- and interindividual variability in presentation. The hallmark neuropathophysiological changes that occur in PD, plus the association between exposure to dopaminergic medications and certain psychiatric disorders, suggest a neurobiological basis for many psychiatric symptoms, although psychological factors are involved as well. There is evidence that psychiatric disorders in PD are still under-recognized and undertreated and although psychotropic medication use is common, controlled studies demonstrating efficacy and tolerability are largely lacking. Future research on neuropsychiatric complications in PD should be oriented toward determining modifiable correlates or risk factors and establishing efficacious and well-tolerated treatment strategies.

Keywords

Anxiety; cognition; dementia; depression; impulse control disorder; Parkinson disease; psychosis

> "Perfect storm: an extremely bad situation in which many bad things happen at the same time."
>
> —Cambridge English Dictionary

INTRODUCTION

James Parkinson may have described depression as a feature of what eventually came to be called Parkinson disease (PD), but careful study of his disease-defining essay finds that none of his six illustrative cases had any neuropsychiatric features. In fact, he made a point to note that cognition was not affected in his patients.[1] It has only been in the past 50 years, with the

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introduction of levodopa and other PD medications and treatments to clinical practice, the increasing lifespan of patients, and increasing awareness and research, that neuropsychiatric disorders and cognitive complications (here combined and called neuropsychiatric symptoms [NPS]), and non-motor symptoms more broadly,[2] have gained recognition as being common, as disabling as motor symptoms, associated with poor long-term outcomes and caregiver burden, and requiring special expertise for optimal management.[3]

By 2020, close to 1 million persons living in the United States will have a diagnosis of PD.[4] Although PD is still considered a movement disorder and is diagnosed based on motor signs and symptoms,[5] the high prevalence of numerous NPS suggests that it is more accurately conceptualized as a neuropsychiatric disorder.[3] In addition to the most commonly studied NPS, such as cognitive impairment (both mild cognitive impairment [MCI] and dementia), depression, and psychosis, other relatively common and clinically significant psychiatric complications include compulsive behaviors diagnosed as impulse control disorders (ICDs), various anxiety symptoms, disorders of sleep and wakefulness, apathy, and fatigue.

This relatively recent, dramatic shift in our understanding of the symptomatology of PD is in part because of the efforts of individual and collaborative research efforts, as well as professional society-led task forces and patient-caregiver organizations. Areas of focus regarding the NPS of PD have included epidemiologic, neurobiological, assessment (diagnostic criteria and assessment instruments) and treatment research, educating patients and families, training treatment providers, and improving the delivery of treatment.

As summarized in the following text, the high cumulative prevalence of a large number of NPS in PD does appear to be the result of a perfect storm, with contributing factors including demographic characteristics, diffuse and multiple neurodegenerative disease pathologies, other neurobiological factors, and PD treatments themselves. Weathering this storm, including adapting to a rapidly changing PD treatment landscape, will require an ongoing, concerted effort with a tripartite focus on research, education/training, and clinical care. Given the now irrefutable evidence that PD is a neuropsychiatric disorder, there ensues a responsibility to respond accordingly to improve the lives of patients.

Cognitive Decline

Of all NPS that can occur in PD, significant cognitive impairment is the most problematic and dreaded. The original assumption, based on early cross-sectional studies, was that approximately 30% of patients with PD suffer from PD dementia (PDD), and that the profile of cognitive impairment in PD was distinct from that of Alzheimer disease (AD). Initial cognitive changes in PD were thought to be primarily characterized by impairment in executive abilities and attention, whereas in AD by memory and language impairments. However, it is now recognized that initial impairments in PD occur in a range of cognitive domains, including executive, memory, visuospatial, attentional, and even language functions, even in patients with milder cognitive deficits or MCI.[6–10]

Prospective, long-term studies have now found that dementia may actually occur in up to 80% of PD patients.[11,12] In addition, approximately 25% of non-demented patients have MCI,[9] which has prognostic significance for predicting more rapid conversion to dementia,

both in early[13] and well-established disease,[14] and MCI is also a risk factor for mortality in early PD.[15] A significant percentage (10%−20%) of newly-diagnosed PD patients have cognitive deficits,[16–18] or experience cognitive decline over several years.[19] More recently, changes in cognition have even been reported prior to PD diagnosis[20] in population-based studies.[21,22] Additionally, prospective studies have demonstrated cognitive worsening in individuals with prodromal or at-risk PD (i.e., those having impaired olfaction and dopamine transporter [DAT] deficits[23] or rapid eye movement [REM] sleep behavior disorder [RBD]),[24] and cognitive impairments in the latter population may predict conversion to dementia with Lewy bodies (DLB) rather than PD.[25]

A point of controversy related to cognition in PD pertains to the related disorder of DLB, and whether differences between the two are categorically, or simply dimensionally, different.[26] DLB, which presents with dementia and some combination of parkinsonism, psychosis, and RBD, is hard to distinguish clinically and neuropathologically from PDD, with the exception of increased AD pathology or biomarkers in DLB versus PDD,[27–29] or perhaps alpha-synuclein genetic variability.[30] There remains a controversial “one-year rule” in place, with dementia that precedes or occurs within one year of onset of parkinsonism being labeled as DLB and all other cases being diagnosed as PDD,[31] although recently proposed clinical diagnostic criteria for PD allow for PDD to be diagnosed at disease onset.[5,32]

A range of demographic and clinical correlates and potential risk factors for identifying PD patients at risk for more rapid cognitive decline have emerged, including increasing age and duration of PD (often correlated), male sex (which differentiates PD from AD), “atypical” parkinsonian features (i.e., postural instability gait disorder instead of tremor-dominant features), psychiatric disorders (e.g., psychosis, apathy, depression, and RBD),[33–39] impaired olfaction,[40] autonomic changes (e.g., orthostatic hypotension [OH]),[41] and comorbid vascular disease (e.g., diabetes mellitus, hypertension, and hyperlipidemia).[42]

There have been significant strides made in our current understanding of the neural substrate of cognitive decline in PD. Neuropathological studies have demonstrated that diffuse, cortical, fibrillized alpha-synuclein(i.e., Lewy bodies) appears to be the major contributing pathology to cognitive decline in PD.[43–45] However, at least one-third of PDD patients also have AD-related neuropathological changes at autopsy,[46] with more beta amyloid plaque than tau tangle deposition,[47] and the combination of PD and AD pathology is the best predictor of a lifetime dementia diagnosis.[48] In addition to pathology, AD cerebrospinal fluid (CSF) biomarkers (AB 1–42),[49] genetic risk factors (*APOE ε4*),[50] positron emission tomography amyloid scans,[51] and a structural magnetic resonance imaging AD signature of atrophy, weighted toward medial temporal lobe and hippocampal atrophy,[52] are all associated with cognitive impairment and decline in PD.

Beyond neuropathology, a range of neurotransmitter deficits are associated with cognitive impairment, including acetylcholine,[53] dopamine,[54–56] and norepi-nephrine.[57,58] Besides *APOE ε4*, other genes implicated include brain-derived neurotrophic factor (BDNF) $val^{66}met$,[59] catechol-O-methyltransferase (COMT) $val^{158}met$,[60] microtubule-associated protein tau (*MAPT*) *H1* polymorphisms,[38,61] and glucocerebrosidase (*GBA*).[62] A range of

neuroimaging techniques have found diffuse gray and white matter neurodegeneration, primarily in the medial temporal lobe, parietal lobe, and prefrontal cortex (PFC),[63–67] some suggestion for increase white matter hyperintensities,[68–70] and metabolic deficits[71,72] with cognitive decline in PD, as well as electrophysiological changes measured with electroencephalogram, quantitative electroencephalogram, or magnetoence-phalogram (i.e., overall diffuse slowing, with low peak frequency, high theta power, low beta power and specific patterns of cortical neural synchronization).[73–77] There is also an emerging interest in plasma-based biomarkers, with low epidermal growth factor as one potential predictor of cognitive decline.[78,79] Given the numerous and diverse changes reported earlier, it is likely that pathological and neurochemical heterogeneity underpins cognitive decline in PD,[80] with disruptions to multiple distinct neural networks occurring over time.[81]

A major step forward was taken a decade ago with the creation of an International Parkinson and Movement Disorder Society (IPMDS) dementia task force. Clinical criteria for the diagnosis of PDD[82] and an algorithm for diagnosing PDD[83] were proposed, leading to significant improvements in the validity and reliability of a PDD diagnosis. This was followed by the creation of an IPMDS task force for PD-MCI, which produced both a review article[84] and recommended diagnostic criteria and guidelines, including recommended cognitive testing.[85] This task force has also published research on the predictive validity of PD-MCI criteria for conversion to PDD,[86] and the relative sensitivity of commonly used cognitive tests in non-demented PD patients.[87] In parallel work, several cognitive assessment instruments for different purposes have now been validated for use in PD, including the Parkinson Disease-Cognitive Rating Scale,[88] the Parkinson Neuropsychometric Dementia Assessment,[89] the Scales for Outcomes of Parkinson Disease-Cognition,[90] the Mattis Dementia Rating Scale-2,[91,92] and the Montreal Cognitive Assessment.[93,94] In addition, two PD- and cognition-specific daily function questionnaires have been developed and validated, [95,96] and performance-based functional cognition measures have recently been validated in PD[97] or have been shown to be sensitive to change in a PD-MCI clinical trial.[98]

The management of cognitive impairment has benefitted from treatment strategies developed for AD. Despite this, only one large, positive controlled cholinesterase inhibitor randomized controlled trial (RCT) in PDD has been published,[99] leading to the Food and Drug Administration (FDA) approval of rivastigmine as a treatment of PDD, but this was 15 years ago. Statistically significant, but clinically modest, effects for rivastigmine on a range of primary and secondary outcome measures were observed, and cholinesterase inhibitor treatment was associated with increased nausea, vomiting, tremor, and dizziness. A similar clinical trial of donepezil for PDD produced similar numerical results for cognitive improvement, but because of an outlier site was a negative study based on the primary outcome measure.[100] In two RCTs that included both PDD and DLB patients, memantine was found to be partially beneficial for PDD in one[101] but not the other,[102] although the latter study showed secondary psychiatric benefit in patients with a DLB diagnosis. The treatment landscape for PD-MCI has been no more promising to date, with failed RCTs for both rasagiline[103] and rivastigmine patch,[98] although the latter study showed a secondary, positive effect on a performance-based measure of cognitive functioning.

In terms of PD medications, there is no evidence that choice of the initial PD medication makes a difference in terms of long-term dementia rates,[104,105] but the association between anticholinergic medication use and long-term cognitive decline in PD[106] is a concern given the common use of medications with anticholinergic properties in this population.[107] For non-pharmacological approaches, there is preliminary evidence that cognitive[108] and physical[109,110] training/activity may lead to at least short-term benefit in some cognitive abilities. Given the association between vascular risk factors[42,111] and pathology[112] and cognitive impairment in PD, and the association between both OH[41] and obstructive sleep apnea (OSA)[113,114] and cognitive performance in PD, treating other common medical or non-motor symptoms is important as well.

Depression

Depression has been the most studied of all noncognitive psychiatric disorders in PD,[3] and there have been major advances in characterizing the frequency, clinical phenotype, and diagnosis. Instead of considering depressed PD (dPD) patients as a homogenous group, recent epidemiologic research has reported that the frequency of major (i.e., more severe) depression is 5%−20%, with non-major forms of depression(i.e., minor or subsyndromal depression) occurring in an additional 10%−30% of patients.[115–118] Therefore, up to 50% of PD patients experience depression at some point in the course of their illness. Yet there is evidence that dPD remains under-recognized and undertreated,[119] even in specialty care settings.[120,121]

Another advance is our understanding of the numerous correlates or possible risk factors for dPD, including female sex,[116] a personal[122] or familial[123] history of depression, early-onset PD,[124] “atypical” par-kinsonism,[117] and psychiatric comorbidity (e.g., worse cognition, psychosis, anxiety, apathy, fatigue, and insomnia).[116,125–128] There is inconsistent evidence that dPD is distinct from non-PD depression; some studies report higher rates of anxiety, pessimism, suicide ideation without suicide behavior, and less guilt and self-reproach in dPD compared with their non-PD counterparts.[129] However, overall predictors of depression are similar in both populations.[130] Not surprisingly, core non-somatic symptoms of depression discriminate most highly between depressed and non-depressed patients (i.e., less likelihood of symptom overlap).[131] It has almost become dogma that suicide is uncommon in PD,[132,133] perhaps related to personality traits (e.g., high neuroticism and harm avoidance, and low open-ness, extraversion, and novelty) thought to characterize PD patients overall,[134,135] although the notion of a par-kinsonian personality remains controversial, largely owing to concerns of recall bias in studies performed post-PD diagnosis. Yet more recent research challenges this and suggests that both death ideation and suicide ideation, if not completed suicide, may be relatively common.[136]

Depression in PD likely results from a complex interaction of psychological, physical/neurologic, and neurobiological factors. The strong association between frequency of depression and severity of PD underscores the impact of disease-related functional impairments.[137,138] Similar rates of depression in PD and equally disabled patients with other diseases indicates that psychological factors are also important.[139] Finally, supporting the contribution of neurobiological factors are findings that depression may be a prodromal

syndrome in some PD patients.[140–142] Biologically, dPD may be related to dysfunction in: 1) subcortical nuclei and the PFC; 2) striatal-thalamic-PFC circuits and the basotemporal limbic circuit; and 3) brainstem monoamine and indolamine (i.e., dopamine, serotonin, and norepinephrine) systems.[71,143–150] One study found an association between the *SLC6A15* and *TPH2* genes and depression in PD,[151] but multiple studies examining the serotonin transporter (*SERT*) and *DAT* genes have been inconclusive.

An IPMDS-commissioned task force reviewed and made recommendations for the use of depression rating scales in PD.[152] Around the same time a National Institute of Neurological Disorders and Stroke/National Institute of Mental Health work group suggested provisional diagnostic criteria for dPD,[153] proposing modifications that are similar to those for depression in AD.[154]

Approximately, 20%−25% of PD patients are on an antidepressant at any given time, even de novo, untreated patients,[155] most commonly a selective serotonin reuptake inhibitor (SSRI).[121,156] Relatively few controlled antidepressant studies for dPD have been published. However, there is now evidence from several, relatively recent RCTs that a tricyclic antidepressant (nortriptyline),[157] an SSRI (paroxetine), and a serotonin and norepinephrine reuptake inhibitor (venlafaxine)[158] are all relatively efficacious in the treatment of dPD. However, it must be noted that in the pivotal Study of Antidepressants in PD,[158] the differences between active (paroxetine and venlafaxine) and placebo treatments for dichotomous outcomes (i.e., response and remission rates) were not statistically significant. In another small RCT, atomoxetine (a selective norepinephrine reuptake inhibitor) was not efficacious for depression, but was associated with improvement in global cognitive performance and daytime sleepiness.[159] In terms of the effects of PD medications, a dopamine agonist (DA) (pramipexole) study for depressive symptoms in PD was positive,[160] but an initial suggestion of an antidepressant effect for an monoamine oxidase B (MAO-B) inhibitor (rasagiline) in PD[155] was followed by a failed RCT for depressive symptoms.[161] Regarding non-pharmacological approaches, cognitive-behavioral therapy (CBT) has been shown to be efficacious for dPD,[162] a positive development given that many dPD patients may prefer psychotherapy, do not respond to pharmacotherapy, or are reluctant to take another medication.[163] Finally, for severe, treatment-refractory dPD, electroconvulsive therapy has been shown to be effective, with the added benefit of temporary improvement in parkinsonism.[164]

Psychosis

Although PD psychosis (PD-P) (hallucinations or delusions) was thought to occur in less than 10% of untreated PD patients and was uncommon prior to the introduction of dopamine replacement therapy (DRT),[165] recent research using a detailed psychiatric interview suggested a high prevalence rate (42%) for minor hallucinations in newly diagnosed, untreated patients,[166] although these findings require replication. In addition, a prospective study that encompassed currently available PD treatments reported a long-term cumulative prevalence of 60%.[167]

Psychosis is associated with reduced quality of life[168,169] and worse prognosis.[170] Psychotic symptoms are an independent predictor of increased mortality in PD,[171] and are also the

single greatest risk factor for nursing home placement in patients with PD.[172–174] It is associated with increased caregiver burden; when compared with other symptoms in PD, psychosis has been singled out as the most prominent determinant of caregiver distress.[175] The effects on caregivers include deterioration of physical health, increasing depression scores, and strained social life.[176] Related to increased caregiver burden is the finding that PD-P is also a major cause of hospitalizations and repeat hospitalizations,[177] a significant problem for PD patients as hospitalization often leads to major disruptions in their PD medication regimen and neurologic decline.[178]

Although visual hallucinations are most commonly reported in PD, it is now recognized that auditory, tactile, and olfactory hallucinations are also relatively common.[179] Correlates or risk factors include exposure to PD medications,[180] older age,[126] and greater cognitive impairment,[127] including dementia.[181] In addition, the overwhelming majority of PD-P patients also report disturbances of sleep and wakefulness, including RBD,[182] and it has been theorized that some hallucinations represent a narcolepsy-like REM sleep disorder during daytime hours, with these hallucinations having particular characteristics (e.g., frequent vision of human figures, faces or animals, or scenery of great beauty).[183]

Despite the association between medication exposure and PD-P, the dosage and duration of antiparkin-sonian treatment does not clearly correlate with psychosis,[126,184] and acute, intravenous, high-dose levodopa challenge does not precipitate hallucinations in PD with pre-existing hallucinations,[185] indicating that the etiology of PD-P is complex. One proposed mechanism is that chronic DRT may lead to excessive stimulation or hypersensitivity of mesocorticolimbic D_2/D_3 receptors.[186] Cholinergic deficits and a serotonergic/dopaminergic imbalance using a range of imaging modalities and other neural probes, have also been implicated,[186–188] particularly in the primary visual system and dorsal/ventral visual association path-ways.[189–193] Neurodegeneration of widespread limbic, paralimbic, and neocortical gray matter, including the PFC, is associated with PD-P.[194–196] Although many genes have been examined for an association with PD-P, the results are negative or mixed for all except for *CCK*.[197,198]

An IPMDS task force reviewed psychosis rating scales used in PD, and listed four instruments as “recommended” for use in PD as primary outcome measures in clinical trials including the Neuropsychiatric Inventory (when a caregiver/informed other is available), the Schedule for Assessment of Positive Symptoms (SAPS), the Positive and Negative Syndrome Scale and Brief Psychiatric Rating Scale, and the Clinical Global Impression Scale as a secondary outcome measure.[199] A recent pivotal trial[200] used a different instrument, a PD-modified SAPS called the SAPS-PD.[201]

Management of PD-P is complex. Observational research suggests that management of comorbid medical conditions and discontinuation or decreasing dosages of non-essential medications may be sufficient for many patients, at least in the short-term.[202] PD medications are usually discontinued sequentially and gradually (anticholinergics, MAO-B inhibitors, amantadine, DAs, catechol-O-methyltransferase inhibitors, and finally, a reduction in levodopa dosage), although this strategy is expert-recommended as opposed to

evidence-based, and the aforementioned ordering is contentious (e.g., discontinuing MAO-B inhibitors before amantadine and DAs).[203]

In PD-P, several theoretically promising atypical antipsychotic (AP) medications, such as risperidone,[204] olanzapine,[205] and aripiprazole,[206] either have not been assessed in RCTs or have been tried clinically and found to be associated with adverse events, primarily worsening parkinsonism presumably due to dopamine receptor blocking, have precluded their routine prescription. In addition, recent research suggests an increased risk of mortality[207] and physical morbidity[208] in PD patients treated with both typical and atypical APs, similar to what has been reported in AD patients. Among traditional atypical APs, quetiapine is the most commonly used, despite the fact that all controlled clinical trials with reasonable sample sizes have been negative or uninterpretable.[209–211] Three randomized clinical trials showed that low-dose clozapine is efficacious for PD-P,[212–214] yet the drug is rarely used in PD,[215] likely due to required routine blood monitoring for potential agranulocytosis, as well as adverse events such as sedation, OH, and sialorrhea.

There is now an FDA-approved treatment specifically for PD-P, pimavanserin, which is a selective serotonin $_{2A}$ (5-HT$_{2A}$) receptor inverse agonist without dopamine receptor-blocking properties. Pimavan-serin was granted breakthrough therapy designation by the FDA because of the large unmet need in the treatment of PD-P, and was approved on the basis of a single, positive RCT,[200] with a subsequent partially positive (i.e., positive at week 6, but not at week 12) trial in patients with AD psychosis.[216] Given recent controversy concerning the validity and reliability of the primary outcome measure (the SAPS-PD), possible delayed response compared with clozapine (2–4 weeks versus 1 week), and unanswered questions about mortality risk, additional research is needed to confirm the efficacy and more fully evaluate the safety and tolerability of pimavanserin in PD-P patients, particularly in patients with comorbid dementia,[217,218] although a secondary analysis of the pivotal PD-P study data found that patients with lower Mini-Mental State Examination scores had a more robust response to pimavanserin.[219]

ICDs and Related Behaviors

This topic has been of increasing importance in PD over the past 15 years, coinciding with the introduction of D2 receptor-selective DAs. ICDs were first reported as a sporadic occurrence in case reports or series,[220] and then characterized epidemiologically and phenomenologically in detail. Initial systematic studies showed that ICDs (i.e., most commonly compulsive and idiosyncratic gambling, buying, sexual behavior, and eating behaviors) occur relatively commonly in treated PD patients,[221,222] and more recent studies confirmed that ICD rates are *not* elevated in de novo, untreated patients.[223] As patients may not report such behaviors to a treating physician, either because of embarrassment, not suspecting an association with PD treatment, or ambivalence regarding ceasing the behavior or treatment, ICDs still remain generally under-recognized in clinical practice,[222] with patient reporting often discrepant from their informed others.[224]

In the largest, international, multisite, cross-sectional study done to date, an ICD was identified in 14% of PD patients, and 29% of those with an ICD had more than one.[225] A recent national multisite study reported a 5-year cumulative ICD incidence rate of 46%,

although the study recruited patients from 2009–2013, before significant changes were made in PD medication prescribing,[226] and another study found clinically significant ICD symptoms in 36% of PD patients with dyskinesias.[227] DA treatment is the strongest PD medication correlate,[225,226] but ICDs may not have their onset until years after DA initiation.[228] Additionally, higher-dose levodopa,[225] amantadine,[229] and MAO-B inhibitor[230] have all been associated with ICDs in PD, although to a lesser extent compared with DA treatment. The effects of DAs do not appear unique to PD patients, as a similar association with ICDs has been reported in restless legs syndrome (RLS),[231,232] fibromyalgia,[233] and prolactinoma or pituitary adenoma[234] patients treated with a DA.

A personal or familial history of alcoholism or gambling, impulsive or novelty-seeking characteristics, young age, male sex, depression and anxiety, and early PD onset have emerged as additional correlates, or potential risk factors, associated with ICDs in PD.[221,225,235] Dopamine dysregulation syndrome (DDS) (or compulsive PD medication use) and other compulsive disorders in PD have also been recognized, particularly in the countries where high doses of levodopa are used.[236] Punding (i.e., repetitive non-goal directed activity) was reported in 14% of PD patients on higher levodopa dosages in one study,[237] but another larger study of unselected PD patients reported a frequency of less than 2%.[238]

A range of cognitive impairments have been reported in PD ICD patients, most commonly executive deficits, including impulsive decision-making and impaired set shifting.[239–242] The dopamine system has been implicated, with both ICD and DDS patients having sensitized D_2/D_3 receptors[243,244] and dysfunction not only in midbrain D_2/D_3 receptors by also extrastriatal (e.g., anterior cingulate cortex) dopamine receptors,[245] and decreased striatal DAT availability in ICD patients.[246] Functional imaging studies have reported altered striatal, cingulate and orbitofrontal activation, and cortico-striatal connectivity, in ICD patients,[247–249] particularly when ICD patients are in an “on” PD medication state.[250] More recent prospective studies have demonstrated that lower striatal DAT availability may be a risk factor for future ICD development,[251] and certain single nucleotide polymorphisms (e.g., serotonin 2A receptor, kappa or mu opioid receptors, and dopamine decarboxylase) previously linked with ICDs in the general population or in PD may also predict incident ICD behaviors with initiation of DRT.[252,253]

Several PD-specific questionnaires and rating scales have been developed for detecting and monitoring ICDs and related behaviors in PD, including the Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease,[254] the Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease-Rating Scale,[255] the Ardouin Scale of Behavior in Parkinson Disease,[256] and the Parkinson Impulse-Control Scale for the Severity Rating of Impulse–Control Behaviors in Parkinson Disease.[257]

In terms of clinical monitoring, as previously mentioned, ICDs may not have their onset until many years after initiation of DA or other PD medication therapy,[228,258] so ongoing, long-term vigilance is required. ICD behaviors often resolve after discontinuing DA treatment.[259] However, some patients do not want to or tolerate DA discontinuation, and a DA withdrawal syndrome with significant physical and psychological symptoms has been

described.[260] The relationship between deep brain stimulation (DBS) and ICDs is complex. Subthalamic nucleus (STN) DBS has been associated with short- and long-term improvement in ICD symptoms,[261–263] most notably when significant decreases in DRT is made postsurgery.[264] However, there is also anecdotal evidence that ICDs may begin or worsen transiently post-DBS surgery,[265] possibly when DRT doses remain high postsurgery.[266] A range of psychiatric treatments (e.g., antidepressants and APs) have been used to treat ICDs in PD, but there is no empirical evidence to support their use in PD patients. A small RCT reported benefit for amantadine as a treatment for pathological gambling in PD,[267] but as previously noted amantadine has been associated with ICDs in a large epidemiologic study.[229] An RCT using naltrexone, an opioid antagonist FDA-approved for alcohol use disorder, was negative on the primary outcome (Clinical Global Impression Scale–Investigator) but positive for change on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease-Rating Scale,[268] and there has been a positive CBT study for ICDs in PD.[269]

Disorders of Sleep and Wakefulness

Remarkably, disorders of sleep and wakefulness have emerged as perhaps the most common nonmotor complications of PD, with up to 90% of patients reporting insomnia (either initiating or maintaining sleep), hypersomnia, sleep fragmentation, sleep terrors, nightmares, nocturnal movements, reductions in non-REM or REM sleep, or RBD.[270,271] RBD, along with impaired olfaction and affective disorders (depression and anxiety), may be a key clinical feature of prodromal PD,[272] with near universal conversion of idiopathic RBD to a Lewy body disorder (PD, DLB, or multiple system atrophy) long term.[273,274] Consistent with idiopathic RBD predicting conversion to DLB in approximately 50% of cases, RBD in the context of PD is also associated with longterm cognitive decline.[275] Other sleep cycle-related disorders occurring in PD are RLS, periodic leg movements in sleep, and OSA,[270] with OSA associated with worse cognitive performance in PD.[276] RBD and other sleep disturbances have been attributed both to progressive degeneration of the cholinergic pedunculopontine nucleus[277] and reduced striatal dopaminergic activity.[278] Associated clinical factors that can disrupt sleep in PD patients are parkinsonism, autonomic symptoms, and psychiatric/cognitive disorders.[33,270,279]

Excessive daytime sleepiness (EDS) (persistent sleepiness) and physical/mental fatigue (tiredness or exhaustion) both are common in PD,[280–282] but the difference and relationship between the two has not been fully delineated. EDS has been attributed variably to impairments in the striatal-thalamic-frontal cortical system, exposure to DRT (especially DAs), and nocturnal sleep disturbances.[270,279] As with RBD, psychiatric comorbidity[280,283] is frequently associated with EDS and fatigue. Daytime “sleep attacks” were first reported toward the end of the last century and were initially attributed to DA treatment, although more recent research suggests they may actually be a manifestation of EDS.[284]

Treatment of disorders of sleep and wakefulness depends on the underlying etiology, and includes adjustment to PD medications (for PD motor symptom-related sleep disturbances, RLS, and periodic leg movements in sleep) and clonazepam (for RBD), although there have been no RCTs for clonazepam in PD RBD in spite of its common use clinically. Melatonin

may improve subjective sleep disturbance and RBD in PD,[285,286] and a controlled trial of eszopiclone (a non-benzodiazepine hypnotic) was partially positive.[287] Evidence has been mixed for modafinil for daytime sleepiness,[288–291] although a recent metaanalysis of three trials showed a significant reduction in sleepiness, as assessed by the Epworth Sleepiness Scale.[292] An RCT of caffeine for EDS in PD was partially positive.[293] Psychostimulants (methylphenidate)[294] are also used clinically for EDS and fatigue in PD. There has been a single, limited quality positive study of continuous positive airway pressure therapy in improving sleep and daytime sleepiness in patients with PD and OSA.[295]

Complications of DBS Surgery

Over the past 15 years, DBS has been used increasingly as a treatment for PD, and in spite of many studies its impact on non-motor symptoms appears to be varied and complex.[296,297] A recent meta-analysis[298] and two controlled studies of DBS versus best medical therapy[299,300] identified significant declines post-DBS in executive functions and verbal learning and memory, not surprising given that DBS electrodes course through the PFC and subcortical white matter when implanted. Cortical point of entry during surgery, passage through the caudate nucleus, and stimulation of particular STN subregions may also increase risk of cognitive impairment post-DBS.[301] Use of model-based stimulation parameters to minimize the spread of current to non-motor portions of the STN reverses the cognitive decline that occurred post-DBS,[302] suggesting that post-DBS cognitive decline may be preventable. In addition, a more recent study of DBS in younger patients with shorter disease duration showed better cognitive tolerability.[303]

In addition to the relationship between DBS and ICDs already discussed, other psychiatric findings post-DBS have included both overall improvement and occasionally worsening of depression, anxiety, psychosis, mania, apathy, and emotional lability.[296] In controlled DBS studies, there were no between-group differences in mood post-DBS surgery,[300,304] and one study reported improvement in anxiety symptoms with DBS.[299] Interestingly, in one controlled study comparing STN with globus pallidus interna DBS, patients who received STN DBS were more likely to experience worsening in both depressive symptoms and processing speed,[305] but meta-analyses of RCTs have come to mixed conclusions on this topic.[306,307] Clinically, pre- and post-DBS psychiatric and cognitive monitoring are important, especially given reports of postsurgical suicide ideation and completed or attempted suicide,[308] although analysis of data from one RCT found no increase in suicide ideation or attempts in the 6-month period after patients were randomized to DBS versus best medical therapy.[309]

Non-Motor Fluctuations

Although motor fluctuations (MFs) (i.e., dyskinesias and “off” periods) have long been recognized as a complication of DRT, only recently has research demonstrated that the majority of patients with MFs also experience non-motor fluctuations (NMFs), including anxiety (e.g., anxiety attacks), slowness of thinking, fatigue, and dysphoria.[310] Furthermore, NMFs are often the more disabling of these complications.[310] The relationship between motor status and NMFs is complex, as there is not always a correlation between affect and motor state,[311,312] and improvements in mood post-levodopa infusion in patients with MFs

can precede improvements in motor status.[313] It remains to be seen if treatments approved on the basis of reducing severity or time of MFs, including newly available longer-acting levodopa or levodopa administered via enteral or oral suspension, also lead to improvements in severity or duration of NMFs.

Other Disorders of Affect

Anxiety—Compared with depression, anxiety in PD has received scant attention to date. Up to 40% of PD patients experience anxiety symptoms or disorders, including generalized anxiety disorder, panic attacks, and social phobia,[314–317] and anxiety and depression symptoms are highly comorbid.[318] Increasing anxiety and discrete anxiety attacks have been associated with NMFs, particularly the onset of "off" periods.[316,317] Similar to depression, there is an increased frequency of anxiety disorders up to 20 years prior to PD onset,[319,320] but other than this clue little is known about the etiology of anxiety in PD. There is now a PD-specific, validated anxiety rating scale, the Parkinson Anxiety Scale.[321] There have been no published RCTs focused on anxiety in PD, and some[157] but not all[158] antidepressant treatment studies have reported secondary benefit for anxiety symptoms. For patients who experience anxiety as part of an "off" state, PD medication adjustments, using FDA-approved medications for MFs, can be made in an attempt to decrease the duration and severity of these episodes. However, some patients require treatment with benzodiazepines (e.g., lorazepam or alprazolam) owing to the disabling nature of their anxiety symptoms, although this medication class must be used cautiously in PD patients because of their propensity to increase sedation, gait imbalance, and cognitive impairment. For non-pharmacologic approaches, CBT techniques can be effective for treating situational anxiety and anxiety attacks.

Apathy—Apathy occurs in approximately 40% of PD patients[322,323] and can occur independently of depression and cognitive impairment, although overlap is common.[322,324] Studies of apathy in PD have reported associations with executive deficits, verbal memory impairment, and bradyphrenia,[322,325] and with decreased cingulate and inferior frontal gyri volumes.[326] There has been one RCT showing benefit for reintroduction of a DA in patients experiencing apathy with DA discontinuation post-DBS surgery,[327] and stimulants (e.g., methylphenidate and amphetamines) are used clinically.

Pseudobulbar affect—Pseudobulbar affect (PBA), also called affective or emotional lability, can occur in a variety of neurodegenerative diseases and neurologic conditions, and prevalence rates of 5%−10% have been reported in PD.[328] Similar to apathy, PBA and depression appear to be overlapping but distinct disorders. Regarding the neuropathophysiology of PBA, a final common pathway appears to be disinhibition of brainstem bulbar nuclei that control the expression of crying and laughing, possibly from impairment in neural path-ways connecting the cortex and brainstem.[329] Numerous small-scale studies have found both tricyclic antidepressants and SSRIs to be efficacious in the treatment of PBA, although none included PD patients,[330] and studies in multiple sclerosis and amyotrophic lateral sclerosis found benefit for the FDA-approved combination of dextromethorphan and quinidine.[331,332] In addition, it is important to educate patients and family members regarding the distinction between PBA and depression.

Global NPS

Recent neuropsychiatric research focuses on global NPS and advanced statistical techniques to delineate neuropsychiatric profiles in PD, to help account for the substantial comorbidity and interindividual het-erogeneity.[333] For instance, in one study that used latent class analysis in a cohort of mild-moderate PD patients, three of the four delineated classes (psychiatric, psychiatric-cognitive, cognitive, and intact) experienced significant, but different, patterns of cognitive and psychiatric symptoms and comprised over two-thirds of patients.[334] Another study using factor analysis found that the first and strongest of four factors included cognitive impairment, psychotic symptoms, depression, and EDS.[335] Finally, a study using cluster analysis and including both broad non-motor and motor symptoms identified four clusters: mild, non-motor dominant, motor-dominant, and severe. In addition, when including only non-motor symptom data, six clusters were identified.[336] This line of research has also established that the burden of global NPS has a significant, detrimental effect on health-related quality of life even in early PD.[337]

Recently, several global assessment instruments have been developed and tested for clinical use in PD, including the Non-Motor Symptoms Scale[338] and the Scales for Outcomes in Parkinson Disease-Psychiatric Complications.[339] The Neuropsychiatric Inventory[340] is commonly used in PD to document the presence and severity of a range of NPS, and the Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale has an expanded Part I that queries about cognitive impairment, psychosis, depression and anxious mood, apathy, and impulse control disorder behaviors, sleep problems, daytime sleepiness, and fatigue.[341] Finally, the IPMDS has commissioned development and validation of a new global, comprehensive non-motor rating scale, including NPS, called the Movement Disorder Society Non-Motor Scale,[342] with the primary validation study now completed.

Landmark Studies and Research Efforts

There have been numerous longitudinal, observational studies and other academic efforts, many ongoing, that have informed our understanding of psychiatric and cognitive complications in PD, including the Sydney Multicenter Study of PD,[12] the Norwegian ParkWest Study Group,[11] the CamPaIGN Study of PD,[38] the DeNoPa Study,[42] the Fox Foundation-funded international PD-MCI Task Force,[86,87] the PD Cognitive Genetics Consortium,[343] the IPMDS Non-Motor PD Study Group, and the Cognitive/Psychiatric (Behavior) Working Group of the Parkinson Study Group.[37,344]

A landmark research study is the Parkinson Progression Markers Initiative (PPMI), conducted by the Michael J. Fox Foundation for Parkinson Research with numerous co-funders and supporting agencies. PPMI is a biomarker-intensive study following a relatively large cohort of de novo PD patients, at-risk PD patients (based on specific genes or having idiopathic RBD), and healthy controls longitudinally. Cognitive findings to emerge from this study include: 1) the prevalence of cognitive impairment in PD patients at baseline varies based on assessment methods used, ranging from 10%−20%; 2) significant cognitive impairment (i.e., dementia) is uncommon in the first 5 years of disease, in part related to the relatively young, highly educated and highly motivated cohort, but using internal (i.e.,

derived from healthy controls) versus published normative data increases sensitivity to detecting initial cognitive decline; 3) there are multiple clinical (e.g., age, olfaction, and RBD symptoms) and biological (e.g., biofluids, CSF, AD biomarkers), neuroimaging (DAT scan, structural magnetic resonance imaging, white matter hyperintensities, and genetics) predictors of cognitive decline in early PD;4) there is significant overlap between cognitive decline in PD and other non-motor symptoms (e.g., olfactory impairment and RBD symptoms); 5) there are modifiable risk factors (e.g., vascular disease) that predict cognitive decline in early PD; and 6) cognitive changes can be detected in general population patients at risk for PD, most notably idiopathic RBD patients.[18,40,68,275,345–352] Psychiatric findings from PPMI include: 1) overall non-motor symptom burden increases significantly over time in early PD, and have clinical predictors (e.g., female sex, older age, and worse PD motor symptoms); 2) affective disorder symptoms (i.e., depression and anxiety) are common in PD and increase slightly in prevalence over the first 5 years of disease; 3) symptoms associated with DRT, particularly chronic or higher-dose exposure (e.g., psychosis and ICDs), remain relatively uncommon in the first 5 years of PD; 4) symptoms of sleep and wakefulness disorders (e.g., insomnia, RBD, and fatigue) increase significantly in frequency over time;5) there are biological predictors of NPS presence or development, including changes in DAT availability, specific genetic single nucleotide polymorphisms, and structural imaging changes; 6) both antidepressant and anxiolytic/sedative-hypnotic medication use are common in early PD (each medication class taken by approximately 25% of patients), and antidepressant use may have an impact on amyloid biomarkers and cognitive course; 7) patients diagnosed with PD but without evidence of dopaminergic deficit have an increase in a range of non-motor symptoms compared with healthy controls; and 8) there are sex differences in several non-motor symptoms in de novo PD, with men predisposed to some and women to others.[18,223,251,252,350,353–359]

CONCLUSION

Some overarching themes have emerged over the past 20 years in our understanding of psychiatric and cognitive complications in PD, including: 1) prospective, longitudinal studies have demonstrated that the cumulative prevalence of most psychiatric and cognitive complications are far higher than earlier cross-sectional studies suggested, with many disorders having a cumulative frequency over 50%, with dementia and sleep disorders likely reaching 80% long term; 2) non-motor complications are associated overall with excess disability, worse quality of life, poorer outcomes (including morbidity and mortality), and greater caregiver burden; 3) there have been significant advances in the assessment (e.g., questionnaires and rating scales) and diagnosis (i.e., consensus diagnostic criteria) of disorders, which has led to improved clinical management and higher quality research; 4) mounting evidence finds that the neural substrate of non-motor complications in PD is a complex interaction of strategically placed PD and other (i.e., AD) neurodegenerative disease pathology, changes in multiple neurotransmitter systems, impairments in neural circuitry subserving mental functioning, and genetic influences; 5) core PD treatments, especially DRT and DBS, have a complex and varied effect on psychiatric symptoms and cognitive abilities; and 6) in spite of the advances highlighted earlier, current treatment

options for the range of disorders discussed, while growing, still remain quite limited, with nearly all efficacious drugs developed or first used for similar conditions in non-PD patients.

Looking ahead, high priority areas for future research in PD include continuing long-term, longitudinal epidemiologic research focused on course and predictors of prevalent and incident psychiatric disorders and cognitive decline; expanding use of sophisticated statistical techniques to re-conceptualize the classification of psychiatric and cognitive disorders, to account for the significant interindividual heterogeneity that occurs; improving recognition and diagnosis through continued development and validation of diagnostic criteria and clinically useful assessment tools that are specific to PD; improving our understanding of the neural substrate of cognitive and psychiatric complications, through examination of neuropathology, disease-specific biomarkers (including developing a positron emission tomography tracer that binds to abnormal or misfolded alpha-synuclein, or even a validated CSF or plasma alpha-synuclein biomarker), neurotransmitters, brain structure, neural circuitry, and genetics; resolving the DLB versus PDD debate, perhaps by using the umbrella clinical diagnosis of Lewy body disorders with subtypes to capture both disorders, or a diagnosis of synuclei-nopathies to also include multiple system atrophy; and conducting large-scale clinical trials to determine the efficacy of different interventions for different psychiatric and cognitive complications, including use of disease-modifying agents (when available) to delay or prevent cognitive and psychiatric complications. Ultimately, reducing the impact of PD on patients and families will require improved recognition and development of better therapies for its numerous and clinically significant neuropsychiatric complications.

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