Neuropsychiatric signs and symptoms in Parkinson disease: lessons learned and looking forward

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SUMMARY
Neuropsychiatric signs and symptoms in Parkinson disease are increasingly recognized as very common throughout the disease course, problematic and equal in importance to motor symptoms. Their presentation can be similar to, or distinct from, their counterparts in the general population. Correlates, and to a lesser extent risk factors, with good predictive value include a mix of demographic, clinical, psychological and psychosocial factors. Their neurobiology is complex and not well understood, with the strongest evidence for disease-induced changes or PD treatments themselves. Ample assessment instruments and formal diagnostic criteria exist, but routine screening lags. Mounting evidence supports a range of pharmacological and non-pharmacological treatments, but efficacious treatment options remain far too limited given the scope and importance of the problem. Optimizing the care of Parkinson disease patients will require additional research, patient education, clinician training, and development of innovative models of clinical care delivery for neuropsychiatric signs and symptoms.

INTRODUCTION

Although motor symptoms remain central to the diagnosis of Parkinson disease (**PD**), neuropsychiatric signs and symptoms (**NPS**) have recently gained recognition as being of equal importance, to the point that PD can be conceptualized as a complex neuropsychiatric disorder. Common NPS fall into broad categories of affect (depression and anxiety), perception and thinking (psychosis), and motivation (impulse control disorders [**ICDs**] and apathy). Recent research, largely cross-sectional but increasing longitudinal, has demonstrated that the prevalence and severity of NPS largely, but variably, increase over time[1], that they can occur in isolation but are frequently polymorbid, and that their etiology is complex. There have been significant advances in our understanding of the neurobiology of NPS in PD, as well as in assessment instruments and diagnostic criteria, but identification and treatment still lag. This review highlights and synthesizes recent developments in the neuropsychiatry of PD (cognitive and sleep disorders excepted) and outlines key unanswered questions and challenges facing the field, with the goal of improving function and quality of life for PD patients.

EPIDEMIOLOGY

Neuropsychiatric signs and symptoms are among the most common non-motor features of PD. Some can occur across the disease course from before sufficient motor symptoms for a PD diagnosis are present (i.e., the prodromal phase[2]) to the late stages, when they are often most severe[3] (**Table 1**). Widely varying prevalence and incidence rates have been reported for NPS in PD, in part reflecting period, cohort and assessment instrument effects.

In terms of conceptualization, it remains controversial if NPS in PD should be considered unique to the disease or "pseudospecific". For instance, whether affective NPS in PD are distinct from those in the general population is not clear. On the other hand, psychosis and ICDs in PD are distinct in many ways from related disorders in the general population. It is also unclear if there remains value in conceptualizing NPS in PD as dopaminergic versus non-dopaminergic in nature. Even features considered at opposite ends of the spectrum of behavioral phenomenology and dopaminergic pathophysiology can overlap (e.g., apathy associated with ICDs[4], and depression with psychosis).

Regarding time of onset, of all NPS depression and anxiety have the highest frequency at disease onset, with depression then rising more rapidly in early disease[5], while clinically-significant psychosis and apathy are associated more with longstanding, late-stage disease, and the timing of ICDs varies and depends on PD medication prescribing practices. There is considerable overlap in NPS, and while particularly in early disease NPS can occur in isolation, they frequently co-occur (e.g., depression often co-occurs with anxiety, apathy overlaps with depression and cognitive impairment, and psychosis and depression can complicate ICDs[6,7]). Thus, in late-stage disease individual NPS are best predicted by the presence of other NPS[3]. As a result of overlapping symptoms, NPS are represented prominently in several recently described clinical endophenotypes (e.g., depressed-anxiety phenotypes[8]). However, none of the non-motor subtypes proposed so far have directly impacted on our understanding of the disease process or management[9].

Depression and anxiety can occur at any disease stage and are commonly reported in the prodromal phase, sometimes years prior to PD diagnosis[2]. While anxiety and depression are also

common in the general population, they are significantly more common in PD, with clinically significant symptoms of depression and anxiety[10] each present in 30-35% of patients overall. Depression and antidepressant treatment are common at disease onset and increase in early disease[5], particularly in those with older-onset disease[1], and approximately 60% of patients with late-stage disease experience depressive symptoms[3]. Anxiety most commonly presents as generalized anxiety disorder, but also as panic attacks, social phobia and agoraphobia[10], and is frequently comorbid with depression. Similar to depression, it can present many years before the diagnosis of PD, but in contrast may be more stable through the disease course[11].

Depression and anxiety are also commonly-reported features of "off" periods (i.e., psychiatric symptoms occurring as part of non-motor fluctuations, **NMFs**, secondary to long-term levodopa treatment), occurring in approximately 35% of patients with this complication[12]. Non-motor fluctuations are psychiatric, cognitive, autonomic or sensory symptoms that vary during the course of the day, typically related to chronic PD medication-induced "on" and "off" periods. Distinguishing persistent affective symptoms from those occurring in the context of "off" periods is not always straightforward, and a given individual can have both. Another syndrome in PD with significant affective symptoms is dopamine agonist (**DA**) withdrawal syndrome (**DAWS**), a complication of DA tapering most commonly reported in the context of ICD management[13].

For psychosis, it is now recognized that "minor" hallucinations (i.e., passage and presence phenomena, and illusions) can occur in early disease[14] and that non-visual hallucinations are common. Overall, minor psychosis occurs in 25-40%, visual hallucinations in 15-30%, non-visual hallucinations (e.g., auditory, tactile and olfactory) in up to 35%, and delusions in 4% of PD patients[15]. Psychosis increases over time[11] and is most common in advanced disease[16], with a cumulative prevalence as high as 60%, and is associated with institutionalization and increased mortality.

Studies show ICD (i.e., excessive gambling, buying, sexual and eating behaviors) rates are *not* elevated in *de novo*, untreated patients), but that that the cross-sectional prevalence is approximately 15% in treated patients[17]. Prevalence rates increase with longer disease duration[18], with a cumulative 5-year incidence rate of 46% reported[19]. Typically, highest rates are reported for eating and lowest for sexual behaviors, as sexual ICD behaviors uncommon in females. An increased risk is reported only in treated patients[20], with the highest risk associated with DAs, and elevated but lesser risks for other medications (e.g., levodopa, amantadine, and MAO-B inhibitors). Dopamine dysregulation syndrome (i.e., **DDS** or compulsive PD medication use) and punding (i.e., repetitive non-goal directed activity) overlap with ICDs but occur primarily with very high levodopa doses. Both ICDs and DDS can overlap with signs and symptoms of bipolar disorder, which has been understudied in PD but appears uncommon.

Apathy in PD has been much less studied than the aforementioned NPS. The reported prevalence ranges widely depending on study design and population, with a mean of 35%. It is comorbid and overlaps symptomatically with depression (i.e., loss of interest is a symptom of both depression and apathy), but remains common even when excluding patients with depression and dementia.

CORRELATES AND RISK FACTORS

Understanding risk factors enables targeted screening of NPS, with increased likelihood of early detection and management, and possibly prevention when risk factors are modifiable. Given how common NPS are in PD, recent research has focused on identifying their correlates (cross-sectional studies) and risk factors (longitudinal studies). For instance, individual studies have implicated numerous demographic[17], clinical[21] and biological[22-24] predictors of ICDs in PD, which need to be verified in large, prospective, multi-site, well-phenotyped, multi-modal studies. However, there is large inter-individual variation in the frequency, time of onset, and severity of NPS in PD. Also, many NPS are also common in the general population, so in PD may have risk factors that are non-PD specific.

Several NPS observed in PD have bidirectional risk associations. For example, there is an increased risk for depression in PD that increases over time, but a diagnosis of mid- or late-life depressive disorder is associated with increased PD risk later in life[25,26]. This suggests that brainstem disease-related pathophysiological changes are responsible for NPS in the prodromal state. Presentation in early, mild disease may also have a psychological or psychosocial contribution, and NPS with onset in later disease may be associated with widespread neuropathology or high total dopamine replacement therapy (**DRT**) exposure. A recent systematic review of longitudinal studies identified several factors associated with risk for multiple NPS, including age, sex, disease severity and DRT[27].

Predictors of depression, from cross-sectional and longitudinal studies, include demographic (i.e., female sex, younger current age), psychiatric (i.e., past or family history of depression, cognitive impairment and REM behavior sleep disorder (**RBD**)), other non-motor (i.e., constipation, pain, upper gastrointestinal symptoms, fatigue), PD-related (i.e., longer disease duration and motor fluctuations), and functional (i.e., impaired activities of daily living and reduced physical activity) factors[27-29](**Table 2**). Psychosocial factors may also play an important role. For instance, spiritual wellbeing, robust social support, access to multidisciplinary medical services and sustained employment may be protective[30,31,28], while inaccurate negative thoughts about the meaning of diagnosis, future progression and perceived social consequences of PD symptoms, as well as low self-efficacy related to one's ability to cope with PD-related challenges, may confer risk. Not surprisingly given the extensive overlap with depression, correlates of anxiety in PD include younger age at disease onset and increasing severity of PD, female sex, cognitive impairment, prior psychiatric history, dysautonomia, sleep-wakefulness disorders, and PD-associated pain and treatment complications (e.g., dyskinesias)[32].

Longitudinal studies suggest that psychosis in PD is most strongly associated with cognitive impairment, older age and longer disease duration, and also with excessive daytime sleepiness, RBD, depression and dyskinesias[27]. There is recent cross-sectional evidence for an association with autonomic dysfunction and visual disturbances[33,34]. Conversely, visual hallucinations are also considered an early marker of future cognitive decline[35]. Regarding DRT, use of DAs is associated with subsequent development of hallucinations[33], as are amantadine, higher levodopa doses, and monoamine oxidase B (MAO-B) inhibitors, with the risk increasing with higher age. However, psychosis may occur independent of DRT, and the risk of psychosis is not the same for all DAs, with continuous apomorphine infusion appearing to have a lower risk[36].

The variables associated with ICDs are higher doses of and longer exposure to DAs, younger age at disease onset, sex (i.e., male for sexual behaviors, female for eating and buying behaviors), family or personal history of substance abuse and higher novelty seeking or impulsivity traits[27,37]; the latter two are also associated with DDS[38]. It has been suggested that DAs with greater dopamine receptor D_3 affinity or immediate release formulations may increase ICD risk, but the evidence is inconclusive. More recently, depression[39] has been associated with incident ICDs, and there is mixed evidence for RBD[40,41]. A recent study found higher rates of ICDs and related behaviors in PD patients treated with DAs and also with co-morbid dementia[42]. The association between ICDs and both deep brain stimulation (**DBS**) and infusion-based therapies for PD is less clear, with the majority of evidence supporting improvement in ICD behaviors post-surgery related to reduction in DRT[43], but also recent reports of new-onset ICD behaviors post-surgery[44].

Regarding apathy, male sex, older age, lower education level, cognitive impairment[45] (particularly executive dysfunction[46]), depression, and more severe PD are independently associated with future occurrence[27,47]. Patients with an ICD who undergo DA tapering are at risk not only of DAWS, but also apathy, including post-DBS surgery. Interestingly, in a recent meta-analysis assessing the correlation between apathy pre- and post-DBS it was shown that apathy increased post-DBS independently of dopaminergic medication changes, disease severity or cognitive performance[48].

As highlighted above, given how common many NPS are in PD, and overlap in their risk factors or correlates, there is frequently polymorbidity among NPS[3]. For instance, recent research found that over 50% of PD patients screen positive for ≥3 NPS by year 5 of the illness[5].

ASSESSMENT

Neuropsychiatric symptoms in PD frequently remain unrecognized and untreated. Underreporting can occur due to lack of insight by the patient or care partner, stigma, poor access to care, and low mental health literacy, but also to clinician underrecognition, because of phenomenological overlap of NPS with motor and other non-motor symptoms[49]. Underdiagnosis for both depression and anxiety is estimated at around 50%; for other NPS few reliable estimates are available.

Therefore, improved recognition of NPS is a critical first step to optimizing care (**Figure 1**). All NPS should be formally assessed by the treating neurologist every 6-12 months, so personalized treatment recommendations can be incorporated into the overarching PD management plan. As patients may not spontaneously report NPS or their severity to providers, care partner input regarding distress and functional impact associated is critically important. Although care partners may also underestimate NPS in patients[50], without their input most ICDs and half of anxiety syndromes would be missed.

In addition to skilled clinical inquiry, systematic assessment of NPS can be done with instruments developed to evaluate NPS globally, screen for specific NPS, or assess NPS severity. A number of validated, PD-specific, global screening instruments for non-motor symptoms are available. The most comprehensive is the International Parkinson and Movement Disorder Society (IPMDS) Non-Motor Rating Scale (MDS-NMS) that rates the frequency and severity of

all NPS discussed herein, including NMFs[51]. Most commonly used historically is the Neuropsychiatric Inventory (NPI), which also captures the perspective of a knowledgeable informant, though this has not been yet been validated for use in PD. These, and other global screening instruments, are listed in **Table 3**.

If global screening measures or the direct inquiry by the clinician reveals presence of symptoms, further assessment can be conducted using disorder-specific rating scales and self-report forms. While these were mostly developed to assess symptom severity, cut-off scores can be applied to detect clinically relevant symptoms. For those instruments that were developed for use in the general population, adjusted cut-off scores are often proposed for PD, to correct for symptom overlap with other PD symptoms (**Table 3**). The IPMDS has a program that reviews the clinimetric properties of rating scales used in PD, which has led to a series of review papers with concrete recommendations, both published[52] and available on the MDS website (https://www.movementdisorders.org/MDS/MDS-Rating-Scales/Rating-Scales-Critiques-and-Recommendations.htm) (**Table 3**).

For routine clinical care, administering the same NPS screening forms (based on clinic or clinician preference) every 6-12 months is sensitive for the detection of symptom change. Self-report scales can be sent to a patient for completion prior to the clinic appointment, or can be completed in the waiting room just prior to the clinical encounter. Any NPS not assessed by the screening instrument(s) should be directly addressed by the provider as part of the clinical interview. For example, a screening packet inclusive of three brief measures, the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part 1, Geriatric Depression Scale (GDS-15), and Parkinson's Anxiety Scale (PAS) can be completed in approximately 10 minutes. As shown in **Table 3**, part 1 of the MDS-UPDRS provides a quick snap-shot of depression, anxiety, psychosis and ICDs, and the GDS-15 and PAS offer a short, yet detailed, assessment of two of the more common and highly treatable NPS that are significantly underreported in routine office visits. Furthermore, any single item score above >1 on the MDS-UPDRS Part 1, or scores >4 on the GDS-15 and >13 on the PAS should trigger a more in-depth evaluation. It is critical to note that the decision whether or not to treat symptoms should ultimately be made in the context of a clinical interview, including focusing on clinically significant distress and functional (e.g., social, occupational) impairment.

The introduction of electronic and mobile health into clinical practice is leading to the development of new assessment methods. The focus is shifting toward obtaining reliable, longitudinal, and individualized information about everyday functioning from patients in real-life situations. Moment-to-moment fluctuations in both motor symptoms and NPS, and their relation to contextual situations, can be assessed with Ecological Momentary Assessments, also known as the Experience Sampling Method[53]. Digital patient-reported outcome measures can be completed by the patient online prior to clinic visits, discussed with the clinician, and used for shared decision-making[54], and smartphones are being used in both traditional and creative ways to detect non-motor symptoms in PD[55].

TREATMENT

Despite the high levels of disability and distress linked to NPS in PD, controlled research regarding their treatment lags far behind advancements made with the management of motor

features, and thus should be regarded as a key unmet need (**Table 4** lists ongoing randomized controlled trials (**RCTs**) for NPS in PD). Effective treatment of NPS has been further stalled by lack of access to PD specialty services and notable PD-specific barriers to mental health care utilization. Given the complex interplay between motor and non-motor symptoms, high rates of NPS comorbidity, and that treatment of one symptom potentially affects other symptoms (e.g., a DRT increase to reduce "off" time potentially increasing psychosis), adequate treatment requires not only specialized clinical expertise in PD, including knowledge of the unique psychosocial challenges faced by patients and families, but also close interdisciplinary collaboration between psychiatry, psychology, and neurology. Moreover, since optimal treatment of every NPS may not be achieveable, especially as PD progresses, management compromises are necessary and require a strong therapeutic alliance, as well as a willingness by the physician to proactively engage patients and families in shared decision making.

Historically, intervention research for NPS in PD has focused on psychopharmacology, and only recently have non-pharmacological treatments (e.g., psychotherapy and exercise) received greater attention[56] (**Figure 2**). A small number of antidepressant RCTs for depression have been conducted to date[57]. Findings support the efficacy and tolerability of several classes of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants, with comparable effect sizes across different drug classes. No class of antidepressants has been shown to significantly worsen motor function. Current evidence does not support the use of reversible, selective monoamine oxidase-B (**MAO-B**) inhibitors as monotherapy for PD depression[58]. Dopamine agonists may confer mood benefit, although the effect size appears small[59,60]. Novel medications, such as nabilone (a synthetic cannabinoid), are still under investigation[61].

Psychological interventions for depression, such as cognitive behavioral therapy (**CBT**), are beneficial in PD. Recently, two separate RCTs of a telemedicine intervention found that a 3-month course of PD-tailored CBT (administered either by phone or web-based video conferencing) was associated with significant improvements in depression compared with usual care[62,63], with results equivalent to those observed in face-to-face trials. Findings on the impact of repetitive transcranial magnetic stimulation (rTMS) for depression have been mixed[56,64]. For severe or refractory depression, electroconvulsive therapy (ECT) can be effective and well tolerated in PD, with the added benefit of temporary improvement in parkinsonism[65]. The impact of other non-pharmacological interventions, such as bright light therapy, and various forms of aerobic training, may also be promising pending further study[66,67]. Ongoing RCTs for depression are diverse in scope and target, with a focus on pharmacotherapy (a large placebo-controlled RCT with nortriptyline and escitalopram), psychotherapy (interpersonal therapy (ITP) and telehealth CBT), and brain stimulation (rTMS and transcranial direct current stimulation (tDCS)).

To date, only a single pharmacological RCT for the treatment of anxiety in PD has been published, a small safety and tolerability study of buspirone (a 5-HT_{1A} partial agonist), in which improvements in anxiety symptoms was offset by poor tolerability[68]. First-line psychopharmacology for anxiety in PD is typically an SSRI, which are also FDA-approved for various anxiety disorders in the general population. Anxiety symptoms in the context of NMFs are first managed with adjustments to the PD treatments, although sometimes it is necessary to

use as-needed or scheduled low-dose benzodiazepines for NMFs and even generalized anxiety symptoms. The first non-pharmacological RCT specifically targeting anxiety in PD found CBT was superior to clinical monitoring in reducing situational anxiety, as well as avoidance behavior and social anxiety[69]. An 8-week mindfulness-based yoga intervention, guided by the theory of self-transcendence, resulted in significant improvements in both anxiety and depression, compared with resistance and strength training exercises[70]. Another area of growing interest is the use of dance-based therapies (e.g., ballet) for a range of non-motor symptoms in PD[71]. Ongoing trials focus on behavior therapy to limit excessive worrying, as well as complimentary and alternative treatments such as acupunture and multistrain probiotics.

Good general management principles for PD psychosis include ruling out delirium, decreasing DRT to the extent possible and minimizing anticholinergic medication use. Cholinesterase inhibitors are sometimes recommended, but a study of its use to prevent incident psychosis was negative[72]. The most notable pharmacological treatment advance for PD psychosis is the antipsychotic pimavanserin, a 5-HT_{2A} receptor inverse agonist/antagonist FDA-approved for PD psychosis and recently shown to be efficacious for dementia-related psychosis, including patients with PD dementia[73]. Quetiapine has little RCT evidence to support its use but remains the most commonly-used antipsychotic in PD, while clozapine is efficacious but rarely used[56]. While clozapine may decrease psychosis severity the most, pimavanserin should be considered first-line given its documented efficacy plus more favorable side-effect profile[74]. Comparator studies are lacking, but a large-scale RCT compaing pimavanserin versus quetiapine is starting soon. Preliminary evidence that antipsychotic use in PD is associated with increased mortality and morbidity risk[75], similar to that reported in Alzheimer disease (**AD**), requires additional study.

Beyond decreasing overall PD medication load, both naltrexone (a nonselective opioid antagonist FDA-approved for the use of alcohol use disorder) and CBT have been explored as management options for ICDs, yielding some positive initial signals in need of further study. An early, small RCT showed a positive effect for amantadine in PD gambling disorder, but subsequent epidemiological evidence suggests that amantadine use is associated with ICDs. RCTs with pimavanserin and clonidine (an alpha-2 receptor agonist) are ongoing. For the treatment of apathy, there is mixed evidence for DA treatment[76], and there is preliminary support for use of acetylcholinesterase inhibitors. Clinically, stimulants (e.g., methylphendiate and amphetamines) are used, although there is no clinical trial support for this.

NEUROBIOLOGY

An improved understanding of the neurobiology of NPS in PD could have downstream clinical benefit, in terms of improved recognition and development of new treatments. Recent preliminary findings that could potentially lead to precision medicine include a clinical-genetic model[23] and a pupillary reward sensitivity measure[22] that predict incident ICD behaviors. However, given disease heterogeneity, multimodal biomarker profiling may be more informative than a single biomarker focus. Regarding treatment, pimavanserin has biological plausibility given the disruption in serotonin pathways with PD psychosis and lack of worsening parkinsonism with this non-dopaminergic antipsychotic.

In addition to key PD pathology (i.e., subcortical Lewy bodies) other neurobiological changes are relevant for the occurrence of NPS. These include diffuse Lewy bodies (i.e., in forebrain,

limbic and neocortical areas); extrastriatal dopaminergic changes; and non-dopaminergic neurotransmitter changes (e.g., cholinergic, serotonergic and adrenergic). In addition, factors such as inflammation, gut-brain axis dysfunction, small vessel disease, and genetics likely contribute. In addition to the specific genes discussed below, there is preliminary evidence that monogenic forms of PD may differ in terms of NPS, with patients with glucocerebrosidase (*GBA*) mutations having a more aggressive course than patients with leucine-rich repeat kinase 2 (*LRKK2*) mutations[77].

Affect

Depression

Supporting the contribution of neurobiological factors are findings that depression, as well as anxiety, can occur in prodromal phase of PD[2]. Biologically, depression in PD may be related to dysfunction in: (1) subcortical nuclei and the prefrontal cortex (**PFC**); (2) striatal-thalamic-PFC circuits and the basotemporal limbic circuit; and (3) brainstem monoamine and indolamine (i.e., dopamine, serotonin, and norepinephrine) systems. Genetic studies have found an association between the *SLC6A15*, *TPH2*[78] and *BDNF* genes[79] and PD depression, but multiple studies examining the serotonin (*SERT*) and dopamine (*DAT*) transporter genes have been inconclusive. Recent studies have found associations with higher α-synuclein burden in the substantia nigra, ventral tegmental area, and nucleus accumbens[80], neuronal loss in substantia nigra pars compacta[81], and changes in brain functional connectivity using EEG[82] and fMRI[83]. Cerebral small vessel disease may also contribute to motor and non-motor symptoms in PD[84]. There is also emerging evidence that microbiome or other gut changes may contribute to depression in PD[85].

Anxiety

Anxiety disorders in the general population are associated with dysfunction in the fear circuit and the limbic cortico-striato-thalamocortical circuit. In PD, increasing severity of anxiety is associated with alterations in the fear circuit (e.g., atrophy of the amygdala and the anterior cingulate cortex; increased functional connectivity between the amygdala and orbitofrontal cortex and hippocampus, and between the striatum and the medial prefrontal cortex, temporal cortex and insula; and reduced functional connectivity between the lateral prefrontal cortex and the orbitofrontal cortex, hippocampus and amygdala). The amygdala has emerged as the central hub of the fear circuit, and disease-related changes in this region (e.g., decreased dopamine transporter (**DAT**) binding and Lewy body/neurite pathology) may contribute to the early and high rates of anxiety in PD[86]. Anxiety in PD is also associated with alterations in the limbic cortico-striato-thalamocortical circuit (e.g., reduced functional connectivity between the striatum and anterior cingulate cortex; reduced dopaminergic and noradrenergic activity in the striatum, thalamus and locus coeruleus; and reduced serotonergic activity in the thalamus)[86].

The dopamine system is linked with anxiety throughout the disease course, from decreased DAT activity in *de novo* untreated patients to an association with NMFs and fluctuating plasma dopamine levels in later-stage disease. However, the relationship between motor status and NMFs is complex, as there is not always a correlation between affect and motor state, and increasing the levodopa dosage does not reliably improve anxiety[87]. Other hypotheses are that dopaminergic alterations in the limbic system, or a dopamine-serotonin imbalance in anxiety-linked regions such as the amygdala or thalamus, contribute to anxiety in PD[87,88].

Perception and thinking

While psychosis in PD has long been associated with DRT, recent research suggests a high prevalence rate for minor hallucinations in *de novo*, untreated patients, highlighting a disease contribution as well[14], in line with the frequent occurrence of visual hallucinations at time of diagnosis in patients with dementia with Lewy bodies (**DLB**). One proposed mechanism is that chronic DRT may lead to excessive stimulation or hypersensitivity of mesocorticolimbic D_2/D_3 receptors. Cholinergic deficits and a serotonin-dopamine imbalance have also been implicated, particularly in the primary visual system and dorsal-ventral visual association pathways, with the $5\text{-}HT_{2A}$ receptor in particular implicated. Neurodegeneration of widespread limbic, paralimbic, and neocortical gray matter, including the PFC, is also associated with PD psychosis[89]. Regarding genetics, some studies have found associations with apolipoprotein (*APOE*) ε4 allele status and *GBA* variants[90], similar to what has been reported for cognitive decline in PD.

Several models, supported by pathological, functional imaging and electrophysiological studies[34], have been proposed to explain the brain mechanisms underlying visual hallucinations (**VH**) specifically. These include the deafferentation-hyperexcitability (altered excitability in the visual associative cortices due to deafferentation), perception and attention deficit (co-occurrence of visuoperceptual and attentional cognitive domain alterations), and attentional control (reduced engagement of the dorsal attention network, greater engagement of the ventral attention network, and intrusion of the default mode network) models[91]. EEG and imaging studies have demonstrated widespread structural, network and connectivity changes associated with VH[91-94]. The changes include higher posterior alpha source activities, hypothesized due to dysfunctions in mesolimbic/mesocortical dopaminergic systems that might reduce the normal slight desynchronizing effect of those systems on parietal-occipital alpha source activities[92]; specific white matter tract changes in posterior thalamic tracts, supporting the association between attentional disturbances and visual hallucinations in PD[93]; thalamic networks with reduced connectivity critical for overall brain integration[94]; and a mega-analysis of cortical thickness and surface area that showed wider cortical involvement underlying VH than previously recognized, including primary visual cortex and surrounding regions, and the hippocampus[91]. Finally, visual disturbances, common in PD, may also merit clinical consideration[95].

Motivation

Impulse control disorders and related behaviors

The dopamine overdose hypothesis posits that DRT in PD improves cognitive abilities dependent on the dopamine-deficient dorsal striatum (i.e., substantia nigra-caudate/putamen pathway), but at the same time impairs cognitive abilities relevant to ICD behaviors and subserved by the intact ventral striatum (i.e., the ventral tegmental area-nucleus accumbens pathway). Both ICD and DDS patients appear to have altered dopamine (D_2/D_3) receptor function not only in the ventral striatum[96], but also downstream dysfunction in extrastriatal regions (e.g., anterior cingulate cortex)[97]. Inconsistent evidence for structural alterations have been found[98,99], while functional imaging studies have reported altered striatal, cingulate and orbitofrontal activation, and cortical-striatal connectivity, in ICD patients[100]. More recent prospective studies have demonstrated differences within the default mode, salience and central executive networks[98]; lower striatal DAT availability[24], and certain single nucleotide polymorphisms (e.g., in serotonin 2A receptor, kappa or mu opioid receptors, and dopamine decarboxylase)[23] predict incident ICD behaviors.

Apathy

Advances have been made in understanding the brain systems underpinning motivated, goal-directed behavior, and the impact of disruptions in these networks (e.g., medial orbitofrontal and anterior cingulate cortices, and the ventral striatum[101]), including in PD. Behavioral studies have convincingly shown that dopamine increases motivated behavior, but also that the motivational deficit observed in PD appears to also involve non-DA pathways or chemicals (e.g., serotonin, norepinephrine, acetylcholine and adenosine[102]). Anatomical and metabolic imaging studies have reported disruptions in limbic circuitry and the PFC[103], and other studies have found corresponding cognitive deficits (i.e., executive impairment)[104].

CONCLUSIONS

Some overarching themes regarding NPS in PD have emerged recently, including: (1) prospective, longitudinal studies have demonstrated that the cumulative prevalence of most NPS are far higher than previously thought, with many having a cumulative frequency greater than 50%; (2) NPS are associated with excess disability, worse quality of life, poorer outcomes, and greater care partner burden; (3) the etiology of NPS in PD is a complex interaction of biological (e.g., PD and other neurodegenerative pathology; multiple neurotransmitter system deficits; impairments in neural circuitry subserving mental functioning; and genetic), psychological and social factors; (4) core PD treatments have varied effects on NPS; (5) advances in assessment and diagnosis have led to higher-quality research and facilitated clinical management; and (6) limited treatment options for NPS that are both efficacious and well-tolerated prevent the optimal management of many PD patients. In spite of significant advances, there remain key unanswered clinical questions (**Panel 1**). Developing and testing new treatments will be challenging since recruitment for clinical trials of NPS in PD is notoriously difficult, in part due to reliance on study sites that are not expert in PD neuropsychiatry, strict inclusion/exclusion criteria, demanding assessment schedules, and a complex population due to the often polymorbid non-motor and motor symptoms. Ideally, there should be a consortium of international PD centers, including those with the ability to evaluate prodromal or at-risk patients applying research criteria[105], dedicated to the study of NPS in PD. The field of PD neuropsychiatry has traveled a long way, but has miles to go before it sleeps.

SEARCH STRATEGY AND SELECTION CRITERIA

In order to help ensure that key recent research studies were included in this review, we searched PubMed (pubmed.gov) to access MEDLINE for articles published in English from January 1, 2015 to June 13, 2021. The systematic review filter was used to narrow the search. MeSH search terms were “Parkinson and depression”; “Parkinson and (psychosis or hallucination or delusion)”; “Parkinson and anxiety”; “Parkinson and (impulse control disorder or dopamine dysregulation syndrome)”; and “Parkinson and apathy”.

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AUTHOR CONTRIBUTION STATEMENTS

DW participated in conceptualization, conducted literature search, wrote draft of manuscript, wrote revisions to manuscript, and wrote response letter to reviewers' comments. DA, KRC, RDD, AFGL, MR-V and AS participated in conceptualization, created draft of manuscript, wrote revisions to manuscript, and wrote response letter to reviewers' comments.

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Table 1. Epidemiology of neuropsychiatric signs and symptoms in Parkinson disease

	Depression	**Anxiety**	**Apathy**	**Psychosis**	**ICD/DDS**
Prevalence	Clinically significant ~35% Major depression ~17%	Point prevalence ~30%	Point prevalence ~35%	Cross-sectional 25-40% Lifetime 50-74%	Cross-sectional 14% 5-yr incidence 45%
Relationship to dopaminergic medication dose	Often improves especially if off-period related	May improve especially if off-period related	May improve especially if off-period related	Typically worsens	Worsens and only occurs on treatment
Relationship to disease severity and stage	Chronic with increase in later stages; prodromal occurrence	Chronic; prodromal occurrence	Increases with disease stage and duration	Increases with disease stage and duration	Increases with disease stage and duration
Prognostic indications	May be associated with later cognitive impairment and mortality	Associated with cognitive decline	Associated with cognitive decline	Institutionalization, dementia, mortality	Unclear

Table 2. Risk factors or correlates for neuropsychiatric signs and symptoms in Parkinson disease

Risk factor	Neuropsychiatric sign or symptom
Younger age or age at PD onset	Depression, anxiety and ICDs
Older age or age at PD onset	Apathy and psychosis
Female sex	Depression, anxiety, psychosis, and compulsive buying and eating
Male sex	Apathy and compulsive sexual behavior
Longer disease duration	Depression and psychosis
Dopamine replacement therapy	ICDs and psychosis
Cognitive impairment	Depression, anxiety, apathy and psychosis
Motor complications	Depression, anxiety, DDS and psychosis
Disorders of sleep and wakefulness	Depression, anxiety and psychosis
Pre-existing personality traits	ICDs
Autonomic dysfunction	Anxiety and psychosis
Visual disturbance	Psychosis
Parkinson's-related pain	Depression and anxiety

Table 3. Selection of most frequently-used general non-motor and NPS-specific screening instruments in Parkinson disease (as reviewed[52] unless otherwise indicated)

General screening instruments for NPS					
	Domains assessed				
Instrument	**Depression**	**Anxiety**	**Psychosis**	**Apathy**	**ICDs**
MDS-UPDRS part 1	X	X	X	X	X
MDS-NMS	X	X	X	X	X
NMSS	X*		X		
NMSQ	X	X	X		X**
NPI***	X	X	X	X	

Syndrome-specific questionnaires				
Syndrome	**Instrument**	**Recommended cut-off**	**Sensitivity (%)**	**Specificity (%)**
Depression	BDI-II	6/7	95	60
	HAMD -17	13/14	88	89
	MADRS	14/15	88	89
	GDS-15	4/5	88	85
	HADS-D	10/11	100	95
	IDS-C	11/12	81	79
	IDS-SR	13/14	90	60
	PHQ-9	6/7	66	80
Anxiety	BAI	12/13	68	75
	HARS	12/13	67	79
	HADS-A	6/7	83	50
	PAS	13/14	71	91
Apathy	AES	38/39	72	82#
	AS	13/14	66	100
	AES-12PD	25/26	96	96##
	AI	na	na	na
	LARS	-14/-13	80	90
Psychosis	PPRS	na	na	na
	PPQ	****	100	92
ICDs	QUIP	any section >1	97	79
	QUIP-RS	10/11	86	84

* NMSS: mood and cognition are combined as one single domain.
** NMSQ: a list of 30 individual questions not grouped into domains. For ICD only increased interest in sex is listed as item.
*** This instrument was not specifically validated in PD.
**** PPQ: any affirmative answer to one of the probing questions.
# Lueken U, Evens R, Balzer-Geldsetzer M, et al. Psychometric properties of the apathy evaluation scale in patients with Parkinson disease. Psychiatry Res 2017;26:e1564.
Stankevich Y, Lueken U, Balzer-Geldsetzer M, et al. Psychometric Properties of an Abbreviated Version of the Apathy Evaluation Scale for Parkinson Disease (AES-12PD). Am J Geriatr Psychiatry 2018;26:1079-90.

Abbreviations (alphabetical): AES = Apathy Evaluation Scale, AI = Apathy Inventory, AS = Apathy Scale, BAI = Beck Anxiety Inventory, BDI-II = Beck Depression Inventory - second version, GDS-15 = 15-item version of the Geriatric Depression Scale, HARS = Hamilton Anxiety Rating Scale, HAMD-17 = 17-item version of the Hamilton Depression Scale, HADS-A = anxiety section of the Hospital Anxiety and Depression Scale, HADS-D = depression section of the Hospital Anxiety and Depression Scale, ICD = impulse control disorders, IDS-C = Inventory of Depressive Symptoms - clinician version, IDS-SR = Inventory of Depressive Symptoms - self-rated, LARS = Lille Apathy Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDS-NMS = Movement Disorder Society – Non-Motor Rating Scale, MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, na = not available, NPI = Neuropsychiatric Inventory, NMSQ = Non-Motor Symptom Questionnaire, NMSS = Non-Motor Symptom Scale, PAS = Parkinson Anxiety Scale, PPQ = Parkinson Psychosis Questionnaire, PPRS = Parkinson Psychosis Rating Scale, PHQ-9 = 9-item Patient Health Questionnaire, QUIP = Questionnaire for Impulsive-compulsive disorders in Parkinson disease, QUIP-RS = Questionnaire for Impulsive-compulsive disorders in Parkinson disease Rating Scale, RHI = Rush Hallucination Inventory.

Table 4. New and recruiting randomized controlled trials for NPS in PD

	Title	ClinicalTrials.gov ID	Primary Outcome	Intervention
1	MST for Parkinson's Disease	NCT04784494	•Depression	•Device: Magnetic Seizure Therapy (MagPro XP MST)
2	Navigated Repetitive Transcranial Magnetic Stimulation for Parkinson's Disease With Depression or Cognitive Impairment	NCT04707378	•Depression	•Device: repetitive transcranial magnetic stimulation(rTMS)
3	Antidepressants Trial in Parkinson's Disease	NCT03652870	•Depression	•Drug: Nortriptyline •Drug: Escitalopram •Drug: Placebo
4	The Effect of Transcranial Direct Current Stimulation (tDCS) on Depression in PD	NCT03227783	•Depression	•Device: transcranial direct current stimulation (tDCS)
5	Exploring Mechanisms for Neuropsychiatric Symptoms of Parkinson Disease Using Transcranial Direct Current Stimulation	NCT03074812	•Depression	•Device: Transcranial Direct Current Stimulation
6	Efficacy of Psychotherapy for Depressed Parkinson's Disease Patients	NCT02552836	•Depression	•Behavioral: Interpersonal Psychotherapy •Behavioral: Supportive Psychotherapy
7	Telehealth Psychotherapy for Depression in Parkinson's Disease	NCT03993041	•Depression	•Behavioral: Cognitive-behavioral therapy (CBT)
8	Acupuncture for Anxiety in Parkinson's Disease	NCT04729010	•Anxiety	•Other: Acupuncture to treat anxiety in Parkinson disease
9	Learning Effective New Strategies for Worry in Parkinson's Disease	NCT04007718	•Anxiety	•Behavioral: Interpretation bias training
10	Treating Anxiety in Parkinson's Disease With a Multi-Strain Probiotic	NCT03968133	•Anxiety	•Dietary Supplement: Probiotic •Dietary Supplement: Placebo
11	Pimavanserin vs. Quetiapine for the Treatment Parkinson's Psychosis	NCT04373317	•Psychosis	•Drug: Pimavanserin •Drug: Quetiapine
12	Randomized Placebo Controlled Trial Evaluating the Efficacy of Pimavanserin, a Selective Serotonin 5HydroxyTryptamine-2A (5HT2A) Inverse Agonist, to Treat Impulse Control Disorders in Parkinson's Disease	NCT03947216	•Impulse Control Disorders	•Drug: Active drug: pimavanserin 17mg (2 strength tablets) •Drug: Placebo: 2 tablets containing same excipients except active compound
13	Study of Clonidine Efficacy for the Treatment of Impulse Control Disorders in Parkinson's Disease:	NCT03552068	•Impulse Control Disorders	•Drug: placebo •Drug: Clonidine

Panel 1. Key unanswered clinical questions for NPS in PD

- **Are more disease-specific assessment tools and diagnostic criteria needed?**
  - Many assessment tools and diagnostic criteria used for NPS in the general population have considerable limitations for use in PD due to overlap between PD features and some NPS, or significant differences in presentation. Recently, some PD-specific rating scales, both for individual and global NPS[51], have been developed.
- **What are nagging clinical management questions?**
  - If NPS are associated with a worse PD course, will treatment impact PD progression, or delay PD onset when in the prodromal state?
  - What is the risk for serotonin syndrome? Antidepressants and reversible, selective MAO-B inhibitors are commonly co-prescribed in clinical practice, and adverse event reporting from an RCT[106] and a retrospective study[107] suggests that the risk is low.
  - Are PD patients at increased risk for completed suicide[108], and does DBS surgery increases this risk[109]?
  - Are NMFs best addressed through adjustments to PD medications, or introduction of psychiatric treatment?
  - Is mortality risk really increased with antipsychotic use in PD, as preliminary retrospective studies suggest[75]?
  - Can modifications to DBS stimulation settings decrease post-operative psychiatric and cognitive side effects[110,111]?
  - Are incident ICDs reported post-DBS surgery related to DBS itself or ongoing high-dose dopaminergic medication use in some individuals[112]?
- **Should treatment focus on individual NPS or overall NPS burden?**
  - Most clinical research studies focus either on a single psychiatric sign or symptom. However, given that NPS in PD are often polymorbid, a case can be made to study NPS more broadly.
- **How can delivery of treatment for NPS in PD be improved?**
  - There is a need for routine, formal screening of NPS in PD, starting at disease onset. In addition, there should be mental health providers with PD expertise who are embedded in PD centers or available for consultation in other settings, in order to provide coordinated pharmacological, psychological and other (e.g., mindfulness yoga, exercise training) treatments for patients. Innovations in telemedicine provide a key opportunity to improve access to specialized treatment for NPS in PD[62,63,113], but development of infrastructure to support virtual care is needed.

Figure 1. Key considerations for the effective assessment of NPS in PD

Figure 2. Management strategies for NPS in PD

CASES

Impulse control disorder

"Ms. F" was diagnosed at age 50 with young-onset idiopathic PD by a movement disorders neurologist after presenting with left upper extremity pain, decreased dexterity, and decreased arm swing; gait stiffness and weakness; rigidity; and prominent depression and anxiety symptoms. She started treatment with pramipexole, a dopamine agonist, at a dosage of 0.25 mg tid, with good motor response. After approximately six months of pramipexole treatment the patient noticed that trips to casinos with friends became more frequent, lasted longer, and involved spending more on slot machines. She started to feel euphoric while gambling. Given that she was by nature conscientious and responsible with no history of problematic gambling, this behavior was out of character. Over the course of the next two years Ms. F's dose of pramipexole was gradually increased to 1 mg tid. During that period, Ms. F gambled away US $1 million. Initially, she gambled with personal money, but eventually began taking money from her family's business and getting loans from credit card companies. Despite understanding that her actions were inappropriate and harmful, she was unable to stop, and her thoughts and desires were consumed with gambling. In addition to compulsive gambling, Ms. F, generally a healthy eater, found herself uncontrollably eating large amounts of junk food, and gained 40 pounds. As with her gambling behaviors, she felt driven to eat and lost enjoyment in food, even when eating her favorite dishes. Feeling despondent Ms. F eventually contacted her neurologist regarding her behaviors and was told that she had a dopamine agonist-induced ICD and to immediately discontinue pramipexole. After just one week she began feeling like her usual self; the drives to gamble and overeat disappeared, and she did not experience acute dopamine agonist withdrawal syndrome symptoms. However, since discontinuing the pramipexole managing her Parkinson's symptoms and mental state has been more challenging. Another dopamine agonist (ropinirole) resulted in similar behaviors and had to be stopped. Her Parkinson symptoms are currently managed with levodopa plus entacapone, resulting in acceptable motor control but dyskinesias and gastrointestinal side effects. Just as importantly, years later after discontinuing pramipexole she still feels the financial and emotional consequences from her time on it. Her family business had to close, she filed for bankruptcy, and her family life has suffered tremendously.

Psychosis

"Ms. P" is currently a 77-year-old female patient diagnosed with PD 11 years ago. She was first treated with a dopamine agonist (pramipexole) with good response, until she developed a hypersexuality ICD. Consequently, this treatment was discontinued, and carbidopa/levodopa was initiated without worsening of the motor response, eventually titrating up to 25/100 3 tablets qid. In addition, the patient had several non-motor symptoms, including depressive symptoms and RBD. Three years ago, she developed aggressiveness and behavioral changes. She started spying on her husband and searching his phone records and messages as part of delusional jealousy. During a holiday travel, she began with paranoid ideas such as the belief that they were being followed by the police to the degree of not wanting to go out of the room. She consulted her neurologist, and an attempt to lower the levodopa dose was unsuccessful. Then an antipsychotic, quetiapine was initiated at 25 mg qd and gradually increased to 100 mg qd, with overall improvement in psychosis. However, about six months later the patient developed anxiety attacks, and the psychosis worsened. Auditory and visual hallucinations now complicated the clinical picture, which also included recurrence of aggressiveness and

negativism. At night she had hallucinations of seeing strangers in her house and hearing them whispering about her. Her hygiene and eating habits deteriorated. She was admitted to the neuropsychiatric ward for inpatient care due to the severity of her symptoms. Neuropsychological assessment included a Mini-Mental State Examination score of 15/30, accompanied by impaired daily functioning, together indicating moderate dementia. Quetiapine was tapered down and discontinued, and clozapine 25 mg qd was started with a significant improvement in symptomatology but not full recovery. Complete blood count was monitored weekly with no evidence of neutropenia. In addition, the patient was started on an antidepressant (venlafaxine) for depressive symptoms and rivastigmine for dementia. On neurological examination she had severe motor fluctuations, freezing of gait and troublesome dyskinesia, and the decision was made to start a device-assisted therapy (apomorphine) with less propensity to cause ICD or psychosis worsening. With this treatment her motor state improved without worsening in NPS.

Non-motor fluctuations

"Mr. C", a 56-year-old male, had a diagnosis of akinesia-dominant PD. Diagnosis was confirmed with a DaTscan showing a diminishing caudate-to-putamen gradient in striatal binding ratios, and over a period of four years the patient was treated with an MAO-B inhibitor (rasagiline) 1 mg and levodopa with decarboxylase inhibitor (100 mg) four times a day. Two years into his condition he started experiencing increasingly intrusive wearing-off periods, characterized by severe mood swings when "off", with depressive spells and anxiety, marked anhedonia, and clouding of mind, all of which improved after next dose of levodopa. Specifically, the depressive spells were evident during early morning "off" period, when at times he felt suicidal and experienced hopelessness, crying, severe anxiety, agitation and restlessness. This also caused significant stress in the care partner, who started to sleep in a different room. One morning his mood was extremely low, and he was suicidal, so he self-referred to his general physician as specialist evaluation was not immediately available. He was seen in the morning during an "off" state and started on an antidepressant, citalopram, for his depression and anxiety symptoms, and received counselling. However, his mood did not improve with citalopram and when next seen by his PD physician he asked to discontinue the medication. He was admitted to hospital for observation, and his motor state monitored with a wearable sensor recording which showed severe bradykinetic periods in the early morning period (between 3-6 AM), as well as up to 7-8 wearing-off episodes during the waking day. His levodopa therapy was augmented by a catechol-O-methyltransferase (COMT) inhibitor (opicapone) and a transdermal dopamine agonist (rotigotine) was also started. As a result of the changes there was a dramatic improvement in amount of "on" time, a significant reduction in early morning "off" periods, and an 80% reduction in daytime "off" periods. "Off" period-related depression and anxiety symptoms resolved on the new PD medication regimen, without the need for specific antidepressant or anxiolytic medication.

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