The neuropsychiatry of Parkinson's disease: advances and challenges

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Abstract

In people with Parkinson's disease, neuropsychiatric signs and symptoms are common throughout the disease course. These symptoms can be disabling and as clinically relevant as motor

symptoms, and their presentation can be similar to, or distinct from, their counterparts in the general population. Correlates and risk factors for developing neuropsychiatric signs and symptoms include demographic, clinical, and psychosocial characteristics. The underlying neurobiology of these presentations is complex and not well understood, with the strongest evidence for neuropathological changes associated with Parkinson's disease, mechanisms linked to dopaminergic therapy, and effects not specific to Parkinson's disease. Assessment instruments and formal diagnostic criteria exist, but there is little routine screening of these signs and symptoms in clinical practice. Mounting evidence supports a range of pharmacological and non-pharmacological interventions, but relatively few efficacious treatment options exist. Optimising the management of neuropsychiatric presentations in people with Parkinson's disease will require additional research, raised awareness, specialised training, and development of innovative models of care.

Introduction

Motor symptoms remain central to the diagnosis of Parkinson's disease, but neuropsychiatric signs and symptoms are gaining recognition as being of similar relevance in many cases, and Parkinson's disease can now be conceptualised as a complex neuropsychiatric disorder. These signs and symptoms fall into broad categories of affect (ie, depression and anxiety), perception and thinking (ie, psychosis), and motivation (ie, impulse control disorders and apathy).

Evidence, mostly from cross-sectional studies and increasingly from longitudinal studies, shows that the prevalence and severity of these neuropsychiatric signs and symptoms often increase over time,[1] that they can present in isolation but are frequently multimorbid, and that their aetiology is complex. There have been substantial advances in the understanding of the neurobiology underlying neuropsychiatric signs and symptoms in Parkinson's disease, and in their assessment instruments and diagnostic criteria, but treatment still lags behind these advances. In this Review, we will synthesise all these developments in the neuropsychiatry of Parkinson's disease (cognitive and sleep disorders excepted) and outline the key unanswered questions and challenges facing this field, with the ultimate goal of improving quality of life for people with Parkinson's disease.

Common psychiatric presentations

Neuropsychiatric signs and symptoms are among the most common non-motor features of Parkinson's disease. However, widely varying prevalence and incidence rates have been reported. These differences partly reflect the time period when the study was conducted, cohort differences, and different effects of the instruments used in their assessment. Some signs and symptoms can occur across the disease course, even before the motor symptoms for a Parkinson's disease diagnosis are present (ie, during the prodromal phase[2]). Signs and symptoms can also occur at advanced disease stages, when they are often most severe.[3]

At early disease stage, signs and symptoms can occur in isolation, although they frequently co-occur (eg, depression often occurs with anxiety, apathy overlaps with depression and cognitive impairment, and psychosis and depression can complicate impulse control

disorders).[4,5] In advanced disease, individual neuropsychiatric signs and symptoms are best predicted by comorbid neuropsychiatric signs and symptoms.[3] Overlapping symptoms are very common and, as a consequence, they have been used to describe clinical endophenotypes (eg, a depressed-anxiety phenotype).[6] However, none of these phenotypes has had any impact on the understanding of the disease process and its management.[7]

Whether the neuropsychiatric presentations of Parkinson's disease should be considered unique to the disease or pseudospecific is controversial (table 1). For instance, it is not clear whether affective symptoms in patients with Parkinson's disease are distinct from those in the general population; however, psychosis and impulse control disorders in patients with Parkinson's disease are distinct from related disorders in the general population. It is also unclear whether classifying these signs and symptoms as dopaminergic versus non-dopaminergic is valuable for clinical or research purposes. Even features considered at opposite ends of the spectrum of behavioural phenomenology and dopaminergic pathophysiology can overlap in some patients (eg, apathy can be associated with impulse control disorders,[8] and depression with psychosis).

Depression and anxiety

At disease onset, depression and anxiety are the most frequently occurring neuropsychiatric signs and symptoms, with depression prevalence rising more rapidly than anxiety in early disease.[9] However, depression and anxiety can also occur at any disease stage.[2] Although common in the general population, they are substantially more common in people with Parkinson's disease, with clinically significant symptoms in 30–35% of patients.[10] Depression is common at disease onset and increases in prevalence throughout the disease course and with age.[1,9] In people with advanced disease, approximately 60% experience depressive symptoms.[3] Anxiety most commonly presents as generalised anxiety disorder, but can also present as panic attacks, social phobia, and agoraphobia,[10] and is frequently comorbid with depression. Anxiety can be more stable in prevalence during the disease course than depression.[11]

Depression and anxiety are also commonly reported features of off periods, occurring as part of non-motor fluctuations, secondary to long-term levodopa treatment, in approximately 35% of patients with this complication.[12] Non-motor fluctuations can be psychiatric, cognitive, autonomic, or sensory, can vary during the course of the day, and are typically related to on and off periods induced by medication. Distinguishing persistent affective symptoms from those occurring in the context of off periods is not always straightforward, and some patients can have both. Another presentation with substantial affective symptoms is dopamine agonist withdrawal syndrome, a complication of tapering of dopamine agonists most commonly reported in the context of management of impulse control disorders.[13]

Psychosis, apathy, and impulse control disorders

It is now recognised that minor hallucinations (ie, 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% of patients with Parkinson's disease, visual hallucinations in 15–30%, non-visual hallucinations (eg, auditory, tactile, and olfactory) in

up to 35%, and delusions in about 4%.[15] The frequency of psychosis increases with disease progression[11] and is most common in advanced disease,[16] with a cumulative prevalence as high as 60%. Psychosis is associated with high risk of hospitalisation, placement in long-term care, and increased mortality.

Both clinically significant psychosis and apathy are often associated with advanced Parkinson's disease, but the timing of impulse control disorders (ie, excessive gambling, shopping, sexual, or eating behaviours) varies, as it depends on dopaminergic medication prescribing practices. Studies show that the rate of impulse control disorders is not elevated in newly diagnosed, untreated patients compared with the general population. However, in cross-sectional studies, the prevalence of impulse control disorders has been estimated as approximately 15% in patients who are receiving parkinsonian treatment.[17] Prevalence rates of impulse control disorders increase with longer Parkinson's disease duration,[18] with a cumulative 5-year incidence rate of 46%.[19] Typically, the highest rates are reported for eating disorders and the lowest for sexual behaviours; sexual impulse control disorders are uncommon in women. An increased risk of impulse control disorders is reported only in patients who have received dopaminergic treatment,[20] with the highest risk associated with dopamine agonists and increased, but lesser risks, for other medications (eg, levodopa, amantadine, and monoamine oxidase B inhibitors). Dopamine dysregulation syndrome (ie, compulsive use of Parkinson's disease medication) and punding (ie, repetitive activity that is non-goal directed) overlap with impulse control disorders, but occur primarily in patients taking very high levodopa doses. Impulse control disorders and dopamine dysregulation syndrome can overlap with signs and symptoms of bipolar disorder, which has been understudied in Parkinson's disease but appears to be uncommon.

Apathy in Parkinson's disease has been much less studied than other neuropsychiatric presentations. The reported prevalence of apathy ranges between studies and depends on study design and population, with an average of 35–40%.[21,22] Apathy occurs with, and overlaps symptomatically with, depression (ie, loss of interest is a symptom of both depression and apathy), but is common even in cohort studies in which patients with depression and dementia are excluded.

Correlates and risk factors

Given how common neuropsychiatric signs and symptoms are in Parkinson's disease, research has focused on identifying their correlates (in cross-sectional studies) and risk factors (in longitudinal studies). The understanding of correlates and risk factors can facilitate targeted screening of neuropsychiatric presentations, increasing the likelihood of early detection and management, and even their potential prevention, when risk factors are modifiable. For instance, some studies have implicated several demographic,[17] clinical,[23] and biological[24–26] predictors of impulse control disorders in Parkinson's disease, which need to be confirmed in large prospective studies. However, there is large interindividual variation in the frequency, time of onset, and severity of neuropsychiatric signs and symptoms in patients with Parkinson's disease. Additionally, they are also common in the general population, so risk factors might not be specific to Parkinson's disease.

Several signs and symptoms observed in Parkinson's disease have bidirectional risk associations. For example, the risk of depression increases over the course of the disease, but a diagnosis of depressive disorder in mid or late life is also associated with an increased risk of Parkinson's disease.[27,28] This association suggests that brainstem pathophysiological changes are responsible for neuropsychiatric presentations in the prodromal phase. Presentation of neuropsychiatric symptoms, particularly depression and anxiety, in early Parkinson's disease can also have a psychological or psychosocial component, and signs and symptoms with onset in advanced disease can be associated with widespread neuropathology or exposure to dopaminergic therapy. A systematic review of longitudinal studies identified several factors associated with risk of neuropsychiatric signs and symptoms, including age (increasing or decreasing with age depending on the disorder), sex (male or female depending on the disorder), disease severity, and dopaminergic therapy.[29]

Predictors of depression, according to evidence from both cross-sectional and longitudinal studies, include demographic (ie, with female sex and younger age associated with increased severity of depression), psychiatric (ie, past or family history of depression, cognitive impairment, and rapid eye movement behaviour sleep disorder), other non-motor (ie, constipation, pain, upper gastrointestinal symptoms, and fatigue), Parkinson's disease-related (ie, longer disease duration and motor fluctuations), and functional (ie, impaired activities of daily living and reduced physical activity) factors (panel 1).[29–31] Psychosocial factors can also have an important role. For instance, spiritual wellbeing, social networks, access to multidisciplinary medical services, and sustained employment might be protective,[30,32,33] while negative thoughts about the meaning of diagnosis, future progression, and perceived social consequences of Parkinson's disease, as well as low self-efficacy related to the patient's ability to cope with Parkinson's disease-related challenges, might confer risk. Given its extensive overlap with depression, correlates of anxiety are similar in Parkinson's disease, and include younger age at disease onset and increasing severity of Parkinson's disease, female sex, cognitive impairment, previous psychiatric history, dysautonomia, sleep and wakefulness disorders, and Parkinson's disease-associated pain and treatment complications (eg, dyskinesias).[34]

Longitudinal studies suggest that psychosis in Parkinson's disease is most strongly associated with cognitive impairment, age (increasing in severity with age), disease duration (increasing in severity with disease duration), excessive daytime sleepiness, rapid eye movement behaviour sleep disorder, depression, and dyskinesias.[29] There is cross-sectional evidence for an association of psychosis with autonomic dysfunction and visual disturbances.[35,36] Conversely, visual hallucinations are also considered an early marker of future cognitive decline.[37] The use of dopamine agonists is associated with subsequent development of hallucinations,[35] as is the use of amantadine, levodopa dose (increasing with dose), and monoamine oxidase B inhibitors, with the risk increasing with age. However, psychosis can occur independent of dopaminergic treatment, and the risk of psychosis is not the same for all dopamine agonists, with continuous apomorphine infusion appearing to have a lower risk than other dopamine agonists.[38]

The risk factors associated with impulse control disorders are high doses of and long exposure to dopamine agonists, young age at disease onset (ie, younger than 60 years), sex (ie, male sex for sexual behaviours and female sex for compulsive eating and shopping behaviours), family or personal history of substance use disorder, and novelty seeking or impulsivity traits.[29,39] Family or personal history of substance use disorder and novelty-seeking or impulsivity traits are also associated with dopamine dysregulation syndrome.[40] It has been suggested that dopamine agonists that have a high affinity for dopamine D_3 receptors or immediate-release formulations can increase the risk of impulse control disorders, but the evidence is inconclusive. Furthermore, depression has been associated with incident impulse control disorders and there is mixed evidence for its association with rapid eye movement behaviour sleep disorder.[41–43] A study found higher rates of impulse control disorders and related compulsive behaviours in patients with Parkinson's disease and dementia who were treated with dopamine agonists than in patients without dementia.[44] The association between impulse control disorders and deep brain stimulation or infusion-based therapies is less clear than that with dopamine agonists, with the majority of evidence supporting improvement in impulse control disorders post-surgery, related to a reduction in dopaminergic therapy,[45] but some evidence shows new-onset impulse control disorders can occur after deep brain stimulation.[46]

Male sex, older age, low education level, cognitive impairment[47] (particularly executive dysfunction[48]), depression, and increasing severity of Parkinson's disease are independently associated with future occurrence of apathy.[29,49] Patients with impulse control disorders who undergo tapering of dopamine agonists after deep brain stimulation are at risk of dopamine agonist withdrawal syndrome and apathy. However, a meta-analysis showed that the severity of apathy, as measured by apathy rating scales, increased after deep brain stimulation, independently of dopaminergic medication, disease severity, or cognitive performance.[50]

Given how common some neuropsychiatric presentations are in Parkinson's disease and how they overlap in risk factors and correlates, there is frequently multimorbidity.[3] For instance, research has found that more than 50% of patients with Parkinson's disease have three or more neuropsychiatric signs and symptoms 5 years after diagnosis.[9]

Instruments for screening and clinical assessment

Neuropsychiatric symptoms are frequently unrecognised and untreated in patients with Parkinson's disease. Under-reporting can occur due to the absence of awareness of the patient or caregiver, stigma, or poor access to mental-health care, but also due to under-recognition from clinicians because of their overlap with motor and other non-motor symptoms (eg, absence of expression; reduced appetite; psychomotor retardation; and insomnia).[51] Underdiagnosis of depression and anxiety is estimated at around 50% in patients with Parkinson's disease, and few reliable estimates are available for other psychiatric presentations.

Therefore, improved recognition is a crucial first step to optimising care. Neuropsychiatric signs and symptoms should be formally assessed by the treating neurologist every

6–12 months in patients with Parkinson's disease, so that personalised treatment recommendations can be incorporated into their management plan. As patients might not spontaneously report symptoms, input from care partners regarding the distress and functional impact of their symptoms is important. Although care givers might also underestimate neuropsychiatric problems,[52] most impulse control disorders and about half of cases with anxiety disorders would be missed without their input.

In addition to skilled clinical inquiry, systematic assessment can be done with several validated screening instruments that are specific for non-motor symptoms of Parkinson's disease. The most comprehensive screening instrument is the International Parkinson and Movement Disorder Society Non-Motor Rating Scale, which rates the frequency and severity of all signs and symptoms discussed in this Review, including non-motor fluctuations.[53] The most commonly used global screening instrument in both research settings and clinical practice is the Neuropsychiatric Inventory, which also captures the perspective of a knowledgeable informant; however, this instrument has not been yet been validated for use in patients with Parkinson's disease. These and other screening instruments are listed in table 2.

If screening measures or the direct inquiry by the clinician reveals the presence of signs and symptoms, additional assessment can be done with disorder-specific rating scales and self-report forms. Although these instruments were mostly developed to assess symptom severity, cutoff scores can be used to detect clinically relevant symptoms. For instruments that were developed for use in the general population, adjusted cutoff scores are often proposed, based on research findings, to correct for overlap with core Parkinson's disease symptoms (table 3). The International Parkinson and Movement Disorder Society has a programme that reviews the clinimetric properties of rating scales, which has led to a series of recommendations.[54]

For routine clinical care, administering the same screening forms (based on the local or physician's preferences) every 6–12 months can detect changes in symptoms. Self-report scales can be sent to a patient for completion before the clinical appointment or can be completed in the waiting room. Any signs and symptoms not assessed by the screening instruments should be directly addressed by the neurologist 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, the Geriatric Depression Scale [GDS-15], and the Parkinson's Anxiety Scale [PAS]) can be completed in approximately 10 min. As shown in tables 2 and 3, part 1 of the MDS-UPDRS provides a quick snapshot of depression, anxiety, psychosis, and impulse control disorders in a patient, and the GDS-15 and PAS offer a short, yet detailed, assessment of two of the more common and highly treatable psychiatric disorders (depression and anxiety) that are under-reported in routine visits. Any single item score above 1 on the MDS-UPDRS Part 1, or scores of 4 or more on the GDS-15 and 13 or more on the PAS, require a more in-depth evaluation. It is crucial to note that the decision of whether or not to treat symptoms should ultimately be made in the context of a clinical interview, focusing on clinically significant distress and functional (eg, social and 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 individualised information about daily functioning from patients in real-life situations. Moment-to-moment fluctuations in motor and neuropsychiatric symptoms, and their relation to contextual situations, can be assessed with ecological momentary assessments, also known as the experience sampling method.[57] Digital patient-reported outcome measures can be completed online by the patient before clinical visits, discussed during the visit, and used for shared decision making,[58] and apps on smartphones are being used to detect both motor and non-motor symptoms (ie, frequent collection of data on mood and cognitive abilities).[59]

Treatment

Despite the high levels of disability and distress linked to neuropsychiatric symptoms in patients with Parkinson's disease, clinical research regarding their treatment lags far behind the advancements made for the management of motor features, and thus should be regarded as a key unmet need in movement disorders. The effective treatment of neuropsychiatric presentations has been further stalled by the absence of specialty services and by notable Parkinson's disease-specific barriers (eg, mobility issues limiting ability to attend weekly in-person psychotherapy sessions) to the use of mental health care. Given the complex interplay between motor and nonmotor symptoms, the high rates of comorbidity, and that treatment of one symptom can affect other symptoms (eg, a dopaminergic therapy increase to reduce off periods can trigger psychosis), adequate treatment requires specialised clinical expertise, including knowledge of the unique psychosocial challenges faced by patients and families, and close interdisciplinary collaboration between psychiatrists, psychologists, and neurologists. Moreover, since optimal treatment might not be achievable, especially as Parkinson's disease progresses, compromises are necessary, requiring a strong therapeutic alliance and engagement of the physician with patients and families in shared decision making.

Historically, research on the neuropsychiatry of Parkinson's disease has focused on psychopharmacology, and only recently have non-pharmacological interventions (eg, psychotherapy or exercise) received attention.[60] A small number of randomised controlled trials of antidepressants for depression have been conducted.[61] Findings support the safety and efficacy of several classes of antidepressants in patients with Parkinson's disease, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants, with comparable effect sizes across drug classes. No class of antidepressants has been shown to significantly impact motor function. Current evidence does not support the use of reversible, selective monoamine oxidase B inhibitors as monotherapy for Parkinson's disease depression.[62] Dopamine agonists might confer a mood benefit, although the effect size appears small.[63,64] Novel medications, such as nabilone (a synthetic cannabinoid), are still being investigated.[65]

Psychological interventions for depression, such as cognitive behavioural therapy, are beneficial in Parkinson's disease. Two randomised controlled trials of a telemedicine intervention found that a 3-month course of cognitive behavioural therapy tailored for

Parkinson's disease (administered either by phone or web-based video conferencing) was associated with statistically and clinically significant improvements in depression compared with usual care,[66,67] with results equivalent to those previously observed in face-to-face trials. Findings on the impact of repetitive transcranial magnetic stimulation for depression have been mixed.[60,68] For severe or refractory depression, electroconvulsive therapy can be effective and well tolerated in patients with Parkinson's disease, with the added benefit of temporary improvement in parkinsonism.[69] The benefits of other non-pharmacological interventions, such as bright light therapy and various forms of aerobic training, are also promising.[70,71] Ongoing trials for depression are diverse in scope and target, and focus on pharmacotherapy (for instance, on nortriptyline and escitalopram), psychotherapy (interpersonal therapy and telehealth cognitive behavioural therapy), or brain stimulation (repetitive transcranial magnetic stimulation and transcranial direct current stimulation). Table 4 lists ongoing randomised controlled trials.

Only a single pharmacological randomised clinical trial for the treatment of anxiety in patients with Parkinson's disease has been published, which was a small safety and tolerability study of buspirone (a serotonin 1A [5-HT$_{1A}$] partial agonist). In this study, improvements in anxiety symptoms were offset by poor tolerability.[72] Front-line psychopharmacology for anxiety in Parkinson's disease is typically a selective serotonin reuptake inhibitor; these drugs are also approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for various anxiety disorders in the general population. Anxiety symptoms in the context of nonmotor fluctuations are first managed with adjustments to the dopaminergic treatments, although sometimes low-dose benzodiazepines are needed for non-motor fluctuations and even generalised anxiety symptoms.

The first non-pharmacological randomised clinical trial specifically targeting anxiety in patients with Parkinson's disease found that cognitive behavioural therapy was superior to clinical monitoring in reducing situational anxiety, avoidance behaviour, and social anxiety.[73] An 8-week mindfulness-based yoga intervention, guided by the theory of self-transcendence, resulted in statistically and clinically significant improvements in both anxiety and depression, compared with resistance and strength training exercises.[74] Another area of growing interest is the use of dance-based therapies (eg, ballet) for a range of non-motor symptoms in Parkinson's disease.[75] Ongoing trials focus on behavioural therapy to limit excessive worrying, and on complementary and alternative treatments, such as acupuncture and multistrain probiotics (table 4).

Good general management principles for Parkinson's disease psychosis include ruling out delirium, decreasing dopaminergic therapy to the extent possible, and minimising anticholinergic medication use. Acetylcholinesterase inhibitors are sometimes recommended, but a study of their use did not show that they were effective.[76] The most notable advance for the pharmacological treatment of psychosis is the use of pimavanserin, a serotonin 2A (5-HT$_{2A}$) receptor inverse agonist and antagonist that is approved by the FDA for Parkinson's disease psychosis and has been shown to be efficacious for dementia-related psychosis, including in patients with Parkinson's disease dementia.[77] Quetiapine has little robust evidence to support its use, but is the most commonly prescribed antipsychotic

in patients with Parkinson's disease, whereas clozapine is efficacious but rarely used.[60] Although clozapine has demonstrated robust decreases in psychosis severity in Parkinson's disease, pimavanserin should be considered as the frontline treatment where available, given its documented efficacy and more favourable tolerability profile.[78] Comparator studies are absent, but a large-scale randomised controlled trial comparing pimavanserin versus quetiapine is starting soon (table 4). The rationale for the use of pimavanserin has biological plausibility, given the disruption in serotonin pathways with Parkinson's disease psychosis and given that this non-dopaminergic antipsychotic does not worsen parkinsonism.[79] Preliminary evidence that antipsychotic use in Parkinson's disease is associated with increased risk of mortality and morbidity,[80] similar to the risk reported in patients with Alzheimer's disease, requires additional study.

Beyond decreasing overall Parkinson's disease medication load, both naltrexone (a non-selective opioid antagonist that is approved by the FDA and EMA for alcohol use disorder) and cognitive behavioural therapy have been explored as management options for impulse control disorders, yielding some positive results that need to be confirmed in further studies (panel 2). An early, small randomised controlled trial showed a positive effect of amantadine in Parkinson's disease gambling disorder,[81] but subsequent epidemiological evidence suggests that amantadine use is associated with increased frequency of impulse control disorders. Trials with pimavanserin and clonidine (an a_2-adrenergic receptor agonist) are ongoing. For the treatment of apathy, there is mixed evidence for the use of dopamine agonists,[82] and there is preliminary support for the use of acetylcholinesterase inhibitors. Clinically, stimulants such as methylphenidate and amphetamines are sometimes used, although there is no evidence from clinical trials for their use.

Neurobiology

An improved understanding of neurobiology can lead to clinical advances, in terms of improved recognition of signs and symptoms, and development of new treatments. Preliminary findings for impulse control disorders that could lead to a personalised treatment approach include a clinical-genetic model[25] (in which patients with Parkinson's disease and impulse control disorders are identified with genetic predictive factors and this information is used, in conjunction with demographic and clinical factors, to guide dopaminergic medication management) and a pupillary reward sensitivity measure[24] (in which participants are instructed to shift their gaze to a visual target as quickly as possible to obtain a reward) that predict incident impulse control disorders behaviours. However, given the heterogeneity in presentations, a multimodal biomarker profiling might be more informative than a single biomarker.

In addition to the Parkinson's disease hallmark pathology (ie, subcortical Lewy bodies), other neurobiological changes are relevant to neuropsychiatric symptoms. These neurobiological changes include diffuse Lewy bodies (ie, Lewy bodies in the forebrain, limbic, and neocortical areas), extrastriatal dopaminergic changes, and non-dopaminergic neurotransmitter changes (eg, cholinergic, serotonergic, and adrenergic changes). Additionally, factors such as inflammation, gut-brain axis dysfunction, small vessel disease, and genetics probably contribute to the emergence of neuropsychiatric

presentations. There is preliminary evidence that monogenic forms of Parkinson's disease might vary in terms of neuropsychiatry, with patients with *GBA* mutations having more severe symptoms and rapid progression than patients with *LRKK2* mutations.[83]

Disorders of affect

Depression—Supporting evidence for a neurobiological substrate comes from studies that show that depression and anxiety can occur in the prodromal phase of Parkinson's disease.[2] Biologically, depression could be related to dysfunction in: subcortical nuclei and the prefrontal cortex; striatal-thalamic-prefrontal cortex circuits and the basotemporal limbic circuit; and brainstem monoamine and indolamine (ie, dopamine, serotonin, and norepinephrine) systems. Genetic studies have found an association between genetic variants in *SLC6A15, TPH2*,[84] and *BDNF*[85] and Parkinson's disease depression, but multiple studies examining serotonin and dopamine transporter genes have been inconclusive. Studies have found associations with increased α-synuclein deposition in the substantia nigra, ventral tegmental area, and nucleus accumbens,[86] neuronal loss in the substantia nigra pars compacta,[87] and changes in brain functional connectivity with EEG and functional MRI.[88,89] Cerebral small vessel disease might also contribute to motor and non-motor symptoms in Parkinson's disease.[90] Additionally, there is emerging evidence that changes in the microbiome or other gut changes might contribute to depression in Parkinson's disease.[91]

Anxiety—Anxiety disorders in the general population are associated with dysfunction in the fear circuit and the limbic cortico-striato-thalamocortical circuit. In Parkinson's disease, the severity of anxiety is associated with alterations in the fear circuit—eg, atrophy of the amygdala and the anterior cingulate cortex; increased functional connectivity between the amygdala, 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 (eg, decreased dopamine transporter binding and Lewy body or neurite pathology) might contribute to the high rates of anxiety in patients with early Parkinson's disease.[92] Anxiety in Parkinson's disease is also associated with alterations in the limbic cortico-striato-thalamocortical circuit—eg, 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.[92]

Impairments in the dopamine system can be linked with anxiety throughout the disease course, from decreased dopamine transporter activity in newly diagnosed patients who have not been treated to an association with non-motor fluctuations and fluctuating plasma dopamine concentrations in advanced disease. However, the relationship between motor and non-motor fluctuations is complex, as there is not always a correlation between affective disorders and motor symptoms, and increasing the dose of levodopa does not reliably improve anxiety.[87] Other hypotheses pose that dopaminergic alterations in the limbic system

or a dopamine–serotonin imbalance in anxiety-linked regions of the brain, such as the amygdala or thalamus, contribute to anxiety in Parkinson's disease.[93,94]

Perception and thinking disorders

Although psychosis in Parkinson's disease has long been associated with dopaminergic therapy, research suggests a high prevalence rate for minor hallucinations in newly diagnosed patients who have never been treated, highlighting a neuropathological contribution,[14] in line with the frequent occurrence of visual hallucinations at the time of diagnosis in patients with dementia with Lewy bodies. One proposed mechanism is that chronic dopaminergic therapy can lead to excessive stimulation or hypersensitivity of the mesocorticolimbic D_2 and D_3 receptors. Cholinergic deficits and a serotonin–dopamine imbalance have also been implicated in psychosis, particularly in the primary visual system and dorsal-ventral visual pathways, with the involvement of 5-HT_{2A} receptors. Neurodegeneration of widespread limbic, paralimbic, and neocortical grey matter, including the prefrontal cortex, is also associated with Parkinson's disease psychosis.[95] Regarding genetics, some studies have found associations with the *APOE* ε4 allele and *GBA* variants,[96] similar to those reported for cognitive decline in Parkinson's disease.

Several models, supported by pathological, functional imaging, and electrophysiological studies,[36] have been proposed to explain the mechanisms underlying visual hallucinations. These include models of 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, increased engagement of the ventral attention network, and intrusion of the default mode network).[97] EEG and imaging studies have shown widespread structural, network, and connectivity changes associated with visual hallucinations.[97–100] The changes include increased posterior alpha source activities, possibly due to dysfunctions in mesolimbic and mesocortical dopaminergic systems that might reduce the slight desynchronising effect of those systems on parietal-occipital alpha source activities;[98] specific white matter tract changes in posterior thalamic tracts, supporting the association between attentional disturbances and visual hallucinations in Parkinson's disease;[99] thalamic networks with reduced connectivity crucial for overall brain integration;[100] and wider cortical involvement underlying visual hallucinations than previously recognised, including primary visual cortex and surrounding regions and the hippocampus.[97] Finally, eye disease (eg, retinal thinning), common in Parkinson's disease, might also merit clinical consideration when assessing the etiology of visual hallucinations.[36,101]

Motivation disorders

Impulse control disorders and related behaviours—The dopamine overdose hypothesis posits that dopaminergic therapy improves cognitive abilities that are dependent on the dopamine-deficient dorsal striatum (ie, substantia nigra-dorsal striatum pathway), but also impairs cognitive abilities relevant to impulse control disorder behaviours that are subserved by the intact ventral striatum (ie, the ventral tegmental area-nucleus accumbens pathway). Patients with impulse control disorders and dopamine dysregulation syndrome

appear to have altered dopamine (D_2 and D_3) receptor function, not only in the ventral striatum[102] but also downstream dysfunction in extrastriatal regions (eg, anterior cingulate cortex).[103] In patients with impulse control disorders, inconsistent evidence for alterations in brain structure has been found,[104,105] and functional imaging studies have reported altered striatal, cingulate, and orbitofrontal activation, and cortical-striatal connectivity.[106] Additional prospective studies have shown differences within the default mode, salience, and central executive networks;[104] lower striatal dopamine transporter availability;[26] and nucleotide polymorphisms (eg, in *HTR2A, OPRK1,* and DDC)[25] can predict incident impulse control disorder behaviours.

Apathy—Advances have been made in understanding the brain systems underpinning motivated, goal-directed behaviour, and the impact of disruptions in these networks (eg, medial orbitofrontal and anterior cingulate cortices and the ventral striatum[107]), including in Parkinson's disease. Behavioural studies have shown that dopamine increases motivated behaviour, but also that the motivational deficit observed in Parkinson's disease appears to also involve non-dopamine agonist pathways (eg, serotonin, norepinephrine, acetylcholine, and adenosine).[108] Anatomical and metabolic imaging studies have reported disruptions in limbic circuitry and the prefrontal cortex,[109] and other studies have found corresponding cognitive deficits (ie, executive impairment).[110]

Conclusions

Prospective, longitudinal studies have shown that the cumulative prevalence of most neuropsychiatric signs and symptoms in Parkinson's disease are higher than previously thought, with a cumulative frequency greater than 50% in some studies. These signs and symptoms are associated with excess disability, worse quality of life, a range of poorer clinical outcomes, and greater burden for caregivers. Their aetiology is a complex interaction of biological (eg, Parkinson's disease and other neuro-degenerative pathology; multiple neurotransmitter system deficits; impairments in neural circuitry subserving mental functioning; and genetics), psychological, and social factors. Parkinsonian treatments have varied effects on neuropsychiatric symptoms, and advances in assessment and diagnosis have facilitated clinical management. However, optimal management is limited by the existence of few treatment options that are both efficacious and well-tolerated. Regardless of substantial advances, key unanswered clinical questions remain (panel 3).

Developing and testing new treatments will be challenging, since recruitment for clinical trials of neuropsychiatry in Parkinson's disease is notoriously difficult, partly due to their reliance on study sites that do not have expertise in Parkinson's disease neuropsychiatry, strict inclusion and exclusion criteria, demanding assessment schedules, and the added complexity of multimorbid presentations with non-motor and motor symptoms. Ideally, there should be a consortium of international Parkinson's disease centres, including those with the ability to evaluate prodromal people or at-risk patients,[119] dedicated to the study of the neuropsychiatry of Parkinson's disease. The field has progressed, but there remains much work to be done.

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Declaration of interests

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Panel 1:

Correlates or risk factors for the presence of neuropsychiatric signs and symptoms in patients with Parkinson's disease

Risk increasing with younger age at Parkinson's disease onset

- Depression
- Anxiety
- Impulse control disorders

Risk increasing with older age at Parkinson's disease onset

- Apathy
- Psychosis

Female sex

- Depression
- Anxiety
- Psychosis
- Compulsive buying and eating

Male sex

- Apathy
- Compulsive sexual behaviour

Risk increasing with disease duration

- Depression
- Psychosis

Dopamine replacement therapy

- Impulse control disorders
- Psychosis

Cognitive impairment

- Depression
- Anxiety
- Apathy
- Psychosis

Motor complications

- Depression
- Anxiety

- Dopamine dysregulation syndrome

- Psychosis

Disorders of sleep or wakefulness

- Depression

- Anxiety

- Psychosis

Pre-existing personality traits

- Impulse control disorders

Autonomic dysfunction

- Anxiety

- Psychosis

Visual disturbance

- Psychosis

Parkinson's disease-related pain

- Depression

- Anxiety

Panel 2:

Case study of impulse control disorder in a patient with Parkinson's disease

Ms F was diagnosed at age 50 years with young-onset idiopathic Parkinson's disease by a movement disorders specialist (MR-V). She presented with upper-left extremity pain, decreased dexterity, decreased arm swing, gait stiffness and weakness, rigidity, and prominent depression and anxiety. She started treatment with pramipexole, a dopamine agonist, at a dose of 0·25 mg three times a day, with a good motor response. After approximately 6 months of pramipexole treatment, the patient noticed that her trips to casinos became more frequent, lasted longer, and involved spending more on slot machines. She started to feel euphoric while gambling. During the course of the following 2 years, Ms F's dose of pramipexole was gradually increased to 1 mg three times a day. During that period, Ms F gambled away about US $1 million. Initially, she gambled with personal money, but eventually she took money from her family's business and credit card loans. Given that she was a conscientious individual and had no history of problematic gambling, this behaviour was considered out of character. Despite understanding that her actions were inappropriate and harmful, she was unable to stop. Additionally, Ms F, previously a healthy eater, found herself uncontrollably eating large amounts of junk food, and gained 18 kg. As with her gambling, she felt driven to eat and lost enjoyment in food, even when eating her favourite dishes. Feeling despondent, Ms F eventually contacted her neurologist regarding these compulsive behaviours, and the specialist discontinued pramipexole. After a week, her drives to gamble and overeat disappeared; she did not have dopamine agonist withdrawal syndrome. However, after discontinuing pramipexole, managing her motor symptoms and mental health was still challenging. Another dopamine agonist (ropinirole) resulted in similar compulsive behaviours and had to be stopped. Her motor symptoms are currently managed with levodopa and entacapone, resulting in acceptable motor control, but some dyskinesias and gastrointestinal side-effects. Years after discontinuing pramipexole, she still feels the financial and emotional consequences from dopaminergic treatment. Her family business closed and she filed for bankruptcy.

Panel 3:

Research priorities in the neuropsychiatry of Parkinson's disease

Accurate assessment tools and diagnostic criteria

- Although some Parkinson's disease-specific rating scales[53] have been developed, assessment tools and diagnostic criteria used for neuropsychiatric signs and symptoms in the general population have considerable limitations for use in Parkinson's disease due to overlap or differences in presentation between parkinsonian features and some signs and symptoms

Knowledge of the natural history and burden of neuropsychiatric signs and symptoms

- Most clinical research studies focus on a single psychiatric sign or symptom; however, given that presentations are often multimorbid, the case can be made to study these signs and symptoms more broadly

- Does treatment of neuropsychiatric signs and symptoms impact Parkinson's disease progression or even disease onset at prodromal stage?

- Are patients with Parkinson's disease at increased risk of suicide[111] and does deep brain stimulation surgery increase this risk?[112]

New safe and efficacious treatments

- What is the risk for serotonin syndrome? Antidepressants and selective monoamine oxidase B inhibitors are often co-prescribed, and adverse event reporting from a randomised controlled trial[113] and a retrospective study[114] suggests that the risk is low

- Are non-motor fluctuations best addressed through adjustments to Parkinson's disease medications or the introduction of psychiatric medication?

- Is mortality risk increased with antipsychotic use in Parkinson's disease, as preliminary retrospective studies suggest?[80]

- Can modifications to deep brain stimulation settings decrease postoperative psychiatric and cognitive side-effects?[115,116]

- Are incident impulse control disorders reported after deep brain stimulation surgery related to deep brain stimulation or ongoing high-dose dopaminergic medication use?[117]

Improved multidisciplinary care

- There is a need for routine, formal screening of neuropsychiatric symptoms in patients with Parkinson's disease, starting at the diagnosis stage; additionally, mental health providers with Parkinson's disease expertise should be embedded in specialised movement disorders centres, or available for consultation in other settings, to provide coordinated pharmacological,

psychological, and other (eg, mindfulness yoga and exercise training) interventions; innovations in telemedicine provide a key opportunity to improve access to specialised treatment,[66,67,118] but infrastructure to support virtual care is needed

Search strategy and selection criteria

We searched PubMed to access MEDLINE for articles published in English between Jan 1, 2015, to June 13, 2021, using the medical subject headings search terms: "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". The systematic review filter was used to narrow the search.

Table 1:

Neuropsychiatric signs and symptoms in people with Parkinson's disease

	Average prevalence and incidence	Relationship to dopaminergic medication	Relationship to disease severity	Prognosis
Depression	~35% point prevalence; ~17% point prevalence for major depression	Often improves with dopaminergic medication, especially if related to off periods	Chronic and frequent throughout the disease course; might be present at prodromal stage	Might be associated with cognitive impairment and mortality risk
Anxiety	~30% point prevalence	Might improve with dopaminergic medication, especially if related to off periods	Chronic; might be present at prodromal stage	Associated with cognitive decline
Apathy	~35% point prevalence	Might improve with dopaminergic medication, especially if related to off periods or occurred during dopaminergic medication decrease	Incidence increases in advanced disease	Associated with cognitive decline
Psychosis	25–40% point prevalence; 50–60% cumulative incidence during the disease course	Typically worsens with dopaminergic medication	Incidence increases in advanced disease	Increases the risk of institutionalisation, dementia, and mortality
Impulse control disorders and dopamine dysregulation syndrome	14% point prevalence; 46% 5-year cumulative incidence	Worsens and only occurs on dopaminergic medication	Increases with disease severity and duration	Unclear

Table 2:

Most frequently used general non-motor and neuropsychiatric signs and symptoms screening instruments in Parkinson's disease

	Depression	Anxiety	Psychosis	Apathy	Impulse control disorders
Movement Disorder Society Unified Parkinson's Disease Rating Scale (part 1)	X	X	X	X	X
Movement Disorder Society Non-Motor Rating Scale	X	X	X	X	X
Non-Motor Symptom Scale	X[*]	..	X	..	..
Non-Motor Symptom Questionnaire	X	X	X	..	X[†]
Neuropsychiatric Inventory[‡]	X	X	X	X	..

Screening instruments are described in Martinez-Martin and colleagues [54] X indicates that the instrument covers the psychiatric symptom.

[*] Mood and cognition are combined as one single domain.

[†] Only increased interest in sex is listed as item for impulse control disorders.

[‡] Not specifically validated in Parkinson's disease.

Table 3:

Syndrome-specific questionnaires most frequently used to assess neuropsychiatric signs and symptoms in Parkinson's disease

	Recommended cutoff	Sensitivity	Specificity
Depression			
Beck Depression Inventory-2	6/7	95%	60%
Hamilton Depression Scale (17 item)	13/14	88%	89%
Montgomery–Asberg Depression Rating Scale	14/15	88%	89%
Geriatric Depression Scale (15 item)	4/5	88%	85%
Depression section of the Hospital Anxiety and Depression Scale	10/11	100%	95%
Inventory of Depressive Symptoms (clinician version)	11/12	81%	79%
Inventory of Depressive Symptoms (self-rated)	13/14	90%	60%
Patient Health Questionnaire (9 item)	6/7	66%	80%
Anxiety			
Beck Anxiety Inventory	12/13	68%	75%
Hamilton Anxiety Rating Scale	12/13	67%	79%
Hospital Anxiety and Depression Scale (anxiety section)	6/7	83%	50%
Parkinson Anxiety Scale	13/14	71%	91%
Apathy			
Apathy Evaluation Scale[55]	38/39	72%	82%
Apathy Scale[56]	13/14	66%	100%
Apathy Evaluation Scale for Parkinson Disease	25/26	96%	96%
Apathy Inventory	NA	NA	NA
Lille Apathy Rating Scale	−14/−13	80%	90%
Psychosis			
Parkinson Psychosis Rating Scale	NA	NA	NA
Parkinson Psychosis Questionnaire	Any affirmative answer	100%	92%
Impulse control disorders			

	Recommended cutoff	Sensitivity	Specificity
Questionnaire for Impulsive-Compulsive Disorders in Parkinson disease	>1 in any section	97%	79%
Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease-Rating Scale	10/11	86%	84%

NA=not applicable (cutoff scores are not established for these instruments).

Table 4:

New and recruiting randomised controlled trials for neuropsychiatric signs and symptoms in Parkinson's disease

	Primary Outcome	Intervention
Navigated Repetitive Transcranial Magnetic Stimulation for Parkinson's Disease with Depression or Cognitive Impairment (NCT04707378)	Depression (Hamilton Depression Scale, 1 month after intervention)	Repetitive transcranial magnetic stimulation versus sham transcranial magnetic stimulation
ADepT-PD (NCT03652870)	Depression (Beck Depression Inventory 2, 2 months after intervention)	Nortriptyline, escitalopram, versus placebo
The Effect of Transcranial Direct Current Stimulation (tDCS) on Depression in Parkinson's Disease (NCT03227783)	Depression (Beck Depression Inventory, 1 month after intervention)	Active transcranial direct current stimulation versus sham transcranial direct current stimulation
Exploring Mechanisms for Neuropsychiatric Symptoms of Parkinson Disease Using Transcranial Direct Current Stimulation (NCT03074812)	Depression (Montgomery Asberg Scale of Depression, 1 month after intervention)	Active transcranial direct current stimulation versus sham transcranial direct current stimulation
Efficacy of Psychotherapy for Depressed Parkinson's Disease Patients (NCT02552836)	Depression (Hamilton Depression Scale, 3 and 6 months after intervention)	Interpersonal psychotherapy versus supportive psychotherapy
Telehealth Psychotherapy for Depression in Parkinson's Disease (NCT03993041)	Depression (Anxiety and Related Disorders Interview Schedule for Diagnostic and Statistical Manual of Mental Disorders-5, 3 and 5 months after intervention)	Cognitive-behavioural therapy versus waitlist control
Acupuncture for Anxiety in Parkinson's Disease (NCT04729010)	Anxiety (Hamilton Anxiety Scale, 6 points after intervention)	Acupuncture versus sham acupuncture
LENS-PD (NCT04007718)	Anxiety (Acceptability Ratings, 4 weeks after intervention)	Interpretation bias training versus sham training
TAP (NCT03968133)	Anxiety (Parkinson Anxiety Scale, 13 weeks after intervention)	Probiotic versus placebo
C-SAPP Study (NCT04373317)	Psychosis (Clinical Global Impression Improvement Scale-Psychosis, 8 weeks after intervention)	Pimavanserin versus quetiapine
PIMPARK (NCT03947216)	Impulse control disorders (Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease-Rating Scale, 8 weeks after intervention)	Pimavanserin (34 mg) and versus placebo (two tablets containing same excipients except pimavanserin)
ID-CLO (NCT03552068)	Impulse control disorders (Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, 8 weeks after intervention)	Clonidine versus placebo