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Neuropsychiatric symptoms in Parkinson's disease: aetiology, diagnosis and treatment Shoned

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Abstract

Historically, Parkinson's disease (PD) was viewed as a motor disorder and it is only in recent years that the spectrum of non-motor disorders associated with the condition has been fully recognized. There is a broad scope of neuropsychiatric manifestations, including depression, anxiety, apathy, psychosis and cognitive impairment. Patients are more predisposed to delirium and PD treatments give rise to specific syndromes including impulse control disorders, dopamine agonist withdrawal syndrome and dopamine dysregulation syndrome. This article seeks to give a broad overview of the spectrum of these conditions, describe the association with PD disease severity and degree to which dopaminergic degeneration and / or treatment influences symptoms. We highlight useful assessment scales that inform diagnosis and the current treatment strategies can be employed to ameliorate these troublesome symptoms that frequently negatively affect quality of life for people with PD.

Introduction

Idiopathic Parkinson's disease (PD), is the second most common neurodegenerative disorder after Alzheimer's disease. Motorically it is characterized by tremor, rigidity, bradykinesia, and postural instability. Whilst it was historically considered to be a movement disorder, the motor symptoms are now increasingly recognised as representing the 'tip of the iceberg'. The significant underlying burden of non-motor symptoms span neuropsychiatric, sleep, somatosensory and autonomic domains. These can often precede the motor symptoms by years or even decades (Klingelhoefer, 2015) and have a negative effect on quality of life.

Parkinson's has been described as the "quintessential neuropsychiatric disorder" (Weintraub, 2011) which reflects both the scope and commonality of neuropsychiatric symptoms (illustrated in Figure 1) that can be encountered. Whilst these symptoms are common and frequently debilitating, they are under-recognised and invariably have a profoundly negative impact on patients' social functioning and ability to work (Perepezko,

2019). The presence of neuropsychiatric symptoms are associated with overall higher carer burden and, potentially, higher care costs whilst being frequently undeclared by patients (Chaudhuri, 2006; Politis, 2010).

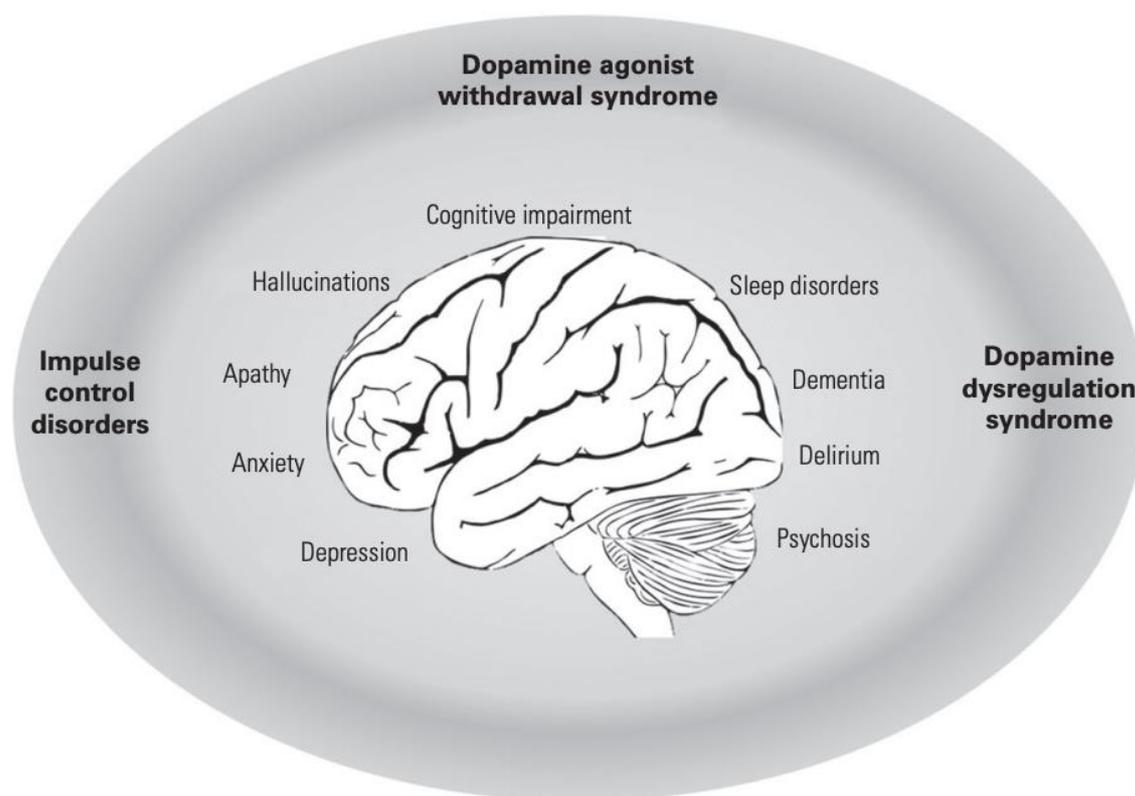


Figure 1: The spectrum of neuropsychiatric disorders in Parkinson's disease. Treatment-related syndromes are indicated in bold text.

In this article we describe the spectrum of neuropsychiatric symptoms that are encountered in Parkinson's necessarily limiting the scope to cover manifestations in idiopathic Parkinson's disease rather than the full spectrum of Parkinsonian syndromes. We describe where the underlying aetiology is understood to result from alpha synuclein pathology and disruption of neurochemical pathways or where adverse effects of treatments can precipitate other manifestations such as impulse control disorders and psychosis. Where assessment scales can be usefully utilized to aid diagnosis and assessment of symptom severity these are included along with the relative strengths and limitations. Whilst a strong evidence base for interventions in some domains is lacking, it is encouraging that literature

in the field is growing year on year (Figure 2). We have sought to provide a pragmatic approach to managing neuropsychiatric issues to tackle the unmet need for better recognition and treatment of these often under-recognised and frequently inadequately managed symptoms.

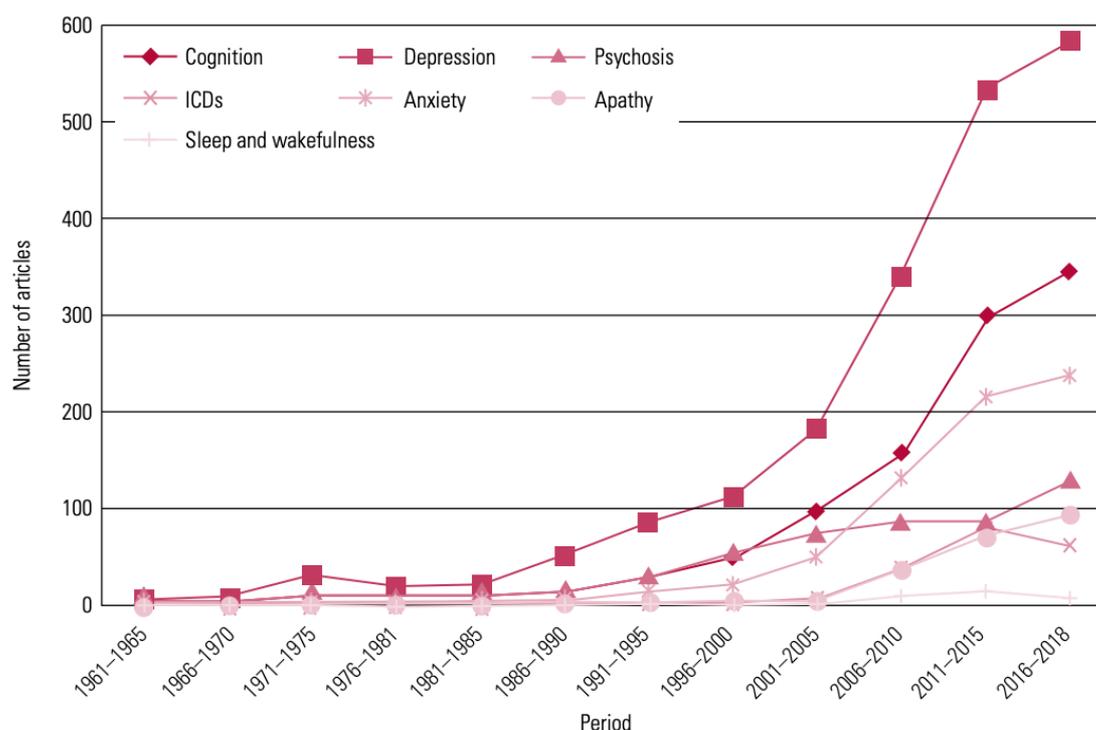


Figure 2: Number of articles published in each neuropsychiatric domain between 1961 and 2018. The PubMed search terms used were: cognition = Parkinson* AND (dementia OR cognitive impairment); depression = Parkinson* AND depression; psychosis = Parkinson* AND (psychosis OR hallucination); impulse control disorders (ICDs) = Parkinson* AND (impulse control disorder OR dopamine dysregulation syndrome); anxiety = Parkinson* AND anxiety; apathy = Parkinson* AND apathy; sleep and wakefulness = Parkinson* AND (insomnia OR sleepiness or fatigue or REM).

Depression

In his original essay on The Shaking Palsy, James Parkinson noted that “A more melancholy object I never beheld” (Parkinson, 1817). Nowadays, depression is still recognised as a common non-motor feature of PD, with the prevalence of clinically significant symptoms being 35% (Reijnders, 2008). A multi-centre study demonstrated that half the study patients were depressed according to the Beck Depression Inventory whilst only 1% had self-reporting symptoms (Findley, 2002; Huse, 2005). There are particular diagnostic challenges which arise from patients’ under-reporting of their depressive symptoms (Dissanayaka,

2011), hypomimia (lack of facial expression), concurrent mood disturbances such as anxiety or apathy (Pagonabarraga, 2015a), psychomotor slowing, as well as under recognition by clinicians (Shulman, 2002). There are a number of validated screening tools available which may be utilized to identify depression in people with PD including the Hamilton Depression Rating Scale (HAM-D), Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Montgomery Asberg Depression Rating Scale (MADRS), and the Geriatric Depression Scale (GDS) all of which are recommended by the International Parkinson and Movement Disorder Society. A working group on depression in Parkinson's recommended that an inclusive approach be taken to symptoms (i.e. regardless of the aetiology) and that motoric 'on' or 'off' state should be considered when making a diagnosis (Marsh, 2006).

The underlying pathophysiology of depression in PD is poorly understood and likely to be multifactorial. A study of almost fifteen hundred patients concluded that higher rates of depression were seen in patients with increasing severity of motor symptoms (Riedel, 2010). Whilst there may be a reactive element to living with a neurodegenerative condition, there is substantial evidence of a neurotransmitter deficit. This biochemical basis is likely mediated through alteration in serotonin, noradrenaline, and acetylcholine. These changes may have a cumulative effect with the hypodopaminergic state with depressive symptoms being more prominent in the motorically 'off' state (van der Velden, 2018). Pharmacological trials have demonstrated an anti-depressant effect with the dopamine agonists pramipexole and ropinirole (Barone, 2010).

The choice of pharmacological therapy is often driven by determination of symptom severity and effect on a patient's quality of life. The options in treating depression in PD are similar to that of depression in any chronic disease state and include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine uptake inhibitors (SNRI), mono-amine oxidase type B inhibitors (MAOBI), and tricyclic antidepressants (TCA). However, there is a paucity of robust randomised controlled trial evidence. SSRIs are most commonly prescribed because of their more favourable side effect profile and lower potential for drug-drug and drug-disease interactions. The use of MOABIs for the motor treatment of PD increases the risk of developing serotonin syndrome through the addition of an antidepressant, although this is rare in clinical practice (Richard, 1997). Whilst the use of TCAs has a potential

advantage in promoting sleep in patients who suffer insomnia, the anticholinergic effects of this drug class and daytime somnolence should be considered. Treatment approaches to depression in PD should ideally be delivered within the framework of a multidisciplinary team who can initiate and monitor pharmacological therapy, provide specific support and expertise.

Apathy

Apathy is one of the most common non-motor features of PD (den Brok, 2015). Increasing efforts have been made within the last decade to distinguish apathy as an isolated mood disorder from apathy as a 'by-product' of depression, although the two symptoms frequently coexist (den Brok, 2015). Apathy may be defined as a "state of reduced motivation with decreased goal-directed behaviours" (Marin, 1991). This may result in low levels of activity, reduced interests and a loss of socialization. The overlap in symptoms between apathy and depression can make diagnosing isolated apathy challenging. There are, however, certain characteristic thoughts and symptoms that are specific to apathy and the presence or absence of these help to confirm the diagnosis. These include emotional indifference and reactivity, reduced activity and interest in the world with a lack of concern for others (Pagonabarraga, 2015b). Depending on the diagnostic criteria used, and the concurrent symptoms of depression and cognitive impairment, the prevalence of apathy ranges from 17-70% in PD (Aarsland, 2009) and, similarly to depression, the symptoms may precede the motor symptoms of PD. The pathophysiology is poorly understood, but may be associated with a neuronal disruption in areas that regulate goal-directed behaviour; mainly dopaminergic projections between the frontal cortex and the ventral tegmentum (Marin, 1991; Carlson, 2011).

The development of diagnostic criteria for apathy has advanced significantly with the development of a task force, commissioned in 2008 by the International Parkinson's and Movement Disorder Society, to assess the clinimetrics of the available rating scales (Shulman, 2016). Subsequent review of the clinimetric properties of 13 scales suggested that the five item WHO Well-being Index (WHO-5) and Neurasthenia Scale detect apathy severity, and the 33-item Lille Apathy Rating Scale (LARS) is valid in the diagnosis 33 items,

while the Starkstein Apathy Scale (SAS) has utility in the exclusion of apathy (Carrozzino, 2019).

There are a range of therapeutic approaches to treating apathy including dopaminergic medications (Marsh, 2006; Chaudhuri, 2013). A double-blind randomized controlled trial comparing the cholinesterase inhibitor rivastigmine with placebo showed a significant improvement in the symptoms of apathy at six months (Devos, 2014).

Anxiety

It is estimated that a third of people with PD experience symptoms of anxiety, which is considered to be a group of disorders consisting of generalized anxiety disorder (GAD), obsessive compulsive disorder, agoraphobia, social phobia, and panic disorder. It can be difficult to distinguish symptoms of anxiety from those of depression or even somatic PD (e.g. sleep disturbances, apathy), which can also be present simultaneously; so, the identification of one should lower the threshold of clinical suspicion for the other.

Classification of these conditions vary in studies, therefore the reported prevalence rates vary, ranging from 3.6% to 55% (Dissanayaka, 2010; Broen, 2016). A systematic review reported the average prevalence of all anxiety disorders in PD to be 31%, with GAD, panic disorder, and social phobia being the most common (Broen, 2016). This wide difference in prevalence may be accounted for by the underreporting of symptoms by patients and under recognition by clinicians.

Researchers will often rely on established criteria, for example from the DSM 4, to make a diagnosis; however, diagnosis in a clinical setting can remain challenging. a study of 42 patients with Parkinson's disease in a university-based movement disorders clinic found that 29% had DSM-III-R anxiety disorder diagnoses, but an additional 40% had anxiety symptoms that did not meet the diagnostic threshold (cited in The DSM-IV criteria can be useful to aid diagnosis but people with anxiety and PD will not invariably meet these criteria. For example, in a university-based movement disorders clinic (n = 42), 29% of subjects with PD had Diagnostic and Statistical Manual of Mental Disorders (DSM)-III anxiety diagnoses, but

an additional 40% had anxiety symptoms that did not meet criteria for a DSM diagnosis (Pontone, 2009). Confirmation of the diagnosis can be challenging because of the overlap between somatic features such as sleep disturbance. Self-reported anxiety scales have been tested in PD, but their clinical utility is uncertain owing to the lack of consensus regarding appropriate cut-off scores (Leentjens, 2008). A detailed patient history and a collateral history are essential but often omitted because of time constraints in clinic. Furthermore, identification can be complicated by the presence of an underlying cognitive impairment. Specific symptoms of anxiety in PD include panic attacks during off periods, excessive worry, and increased subjective motor symptoms. The timing of symptoms can mirror motor fluctuations or manifest in an unrelated pattern (Aarsland, 2009).

Similarly to depression in PD, the aetiology of anxiety is multifactorial. There may well be underlying neurobiological changes that cause anxiety; but so, too, it is likely that there are psychosocial causes in reaction to the burden of having PD. Social anxiety is especially common in the context of the reactive model, with people with PD expressing concern over being negatively perceived in public leading to social withdrawal. Patients may also fear the progression of the disease, disability, institutionalization, and issues surrounding their death. With the high falls risk in the disease, an associated fear of falling can be very prominent (Prediger, 2012).

The role of dopaminergic neurotransmission in the context of anxiety is poorly understood but has been linked to both social phobia and anxiety symptoms in animal models (Prediger, 2012). Serotonergic and noradrenergic systems also have a role in PD anxiety owing to their widespread distribution in the structures involved in emotional modulation. Research demonstrates that people with PD who score higher on anxiety questionnaires have a shorter serotonin transporter allele, highlighting the potential role of neuropsychiatric genetics in this group (Menza, 1990).

Anxiety in PD has a huge impact on quality of life, not only for the patient but also for their family and carers. Social anxiety can lead to isolation in the community that further exacerbates anxiety creating a self-perpetuating cycle. It can also precipitate loneliness, particularly in older people, which can contribute to the subsequent development of

depression. This can in turn affect treatment plans, hindering motivation and engagement in rehabilitation and healthcare services (Prediger, 2012).

There is a paucity of evidence on the management of anxiety in PD. There are no robust clinical trials of either pharmacological or psychological strategies. Anxiety has been assessed as a secondary outcome in depression clinical trials but because of the selection criteria used, any therapeutic effects on anxiety were diluted (Koychev, 2017).

Guidance for managing anxiety in older adults with chronic physical health conditions (Koychev, 2017) can be extrapolated, which places initial emphasis on lifestyle modification, focussing on optimal sleep, exercise, nutrition, and socializing in addition to eliminating any exacerbating medical causes for anxiety such as metabolic anomalies, nutritional deficiencies, and drug reactions. Pharmacological approaches are then advised with the introduction of SSRIs and SNRIs. The use of benzodiazepines is discouraged because of their side effect profile. Behavioural therapies in the form of cognitive behavioural therapy, mindfulness, and desensitization are also of benefit but are reliant on adequate motivation and adherence (Koychev, 2017).

Psychosis

Psychosis in PD is a spectrum of neuropsychiatric manifestations consisting of 'positive' symptoms namely illusions, hallucinations, and delusions (Ravina, 2007). Definitions of psychotic symptoms in the context of PD are consistent with the definitions in the wider psychiatric literature. The prevalence of psychosis also varies depending on the diagnostic tool used. In 2007, the combined National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Mental Health (NIMH) work group proposed a unifying diagnostic criterion for PD psychosis which includes the presence of at least one psychotic symptom (Ravina, 2007). Longitudinally, prevalence increases with disease duration, (Gibson, 2013) and at 12 years 60% of patients from a community cohort reported hallucinations or delusions (Forsaa, 2010).

Proposed risk factors for the development of psychosis in PD includes duration and severity of PD, and cognitive impairment. The development of these symptoms at a time when

demands associated with caring for the people with PD are already high results in a greater sense of burden for the carer in comparison with caring for those without psychosis and is also a predictive factor for nursing home placement (Marsh, 2004). Additional risk factors for psychosis include treatment with dopaminergic and anti-cholinergic medications. The relationship between the use of PD medication and development of PD psychosis remains controversial. Anecdotally, an association between PD psychosis and the use of dopaminergic therapies and duration of treatment has been observed. Psychotic symptoms can develop on initiation of medication with a subsequent improvement with reduction or withdrawal and this is most potently seen with the use of dopamine agonists. None the less, a causal effect of dopaminergic medications has not been established and psychotic symptoms have been described in recently diagnosed patients who have not yet started treatment (Aarsland, 2009).

The initial management of PD psychosis involves the identification and treatment of any precipitating factors. Psychosis may be the manifestation of an acute illness or change in medication and a thorough clinical evaluation is imperative. If the patient is tolerating the symptoms of psychosis with no adverse features, the best approach may be to watch and wait. Many patients with PD do not find hallucinations distressing and retain insight. Where intervention is warranted, there are a number of approaches. In patients with significant cognitive impairment, rivastigmine has good efficacy (Burn, 2006). Clozapine and pimavanserin (a 5-HT_{2A} inverse agonist, not yet licensed for use in the UK) are efficacious (Cummings, 2014). There are barriers for the routine use of clozapine in the clinical setting, namely the regular blood tests required to monitor for agranulocytosis and the registration required for prescribing the drug. Other atypical antipsychotics used in clinical practice include quetiapine, olanzapine, and risperidone, but these can cause worsening of motor symptoms and other side effects including QT prolongation, sedative effects, metabolic syndrome, and a potential deterioration in cognition. The most recent National Institute for Health and Care Excellence (NICE) advocates the use of low-dose quetiapine and clozapine as the most appropriate medications in PD psychosis,(National Institute for Health and Care Excellence, 2017) and in clinical practice at present, quetiapine is commonly used.

Cognitive impairment

Cognitive impairment is a common non-motor manifestation in PD and is heterogeneous in terms of its severity, rate of progression, and the cognitive domains affected. It has a significant negative impact on patients and their carers and is associated with increased disability, mortality (Levy, 2002), carer burden, (Aarsland, 1999) and need for nursing home placement (Aarsland, 2000). Although Lewy body dementia (LBD) is beyond the scope of this article, it is important to mention that both PD dementia (PDD) and LBD share many clinical and neurochemical features despite being two distinct entities. Their diagnosis is based on an arbitrary distinction between the time of onset of dementia in relation to motor symptom onset. In PDD, cognitive impairment presents one or more years after the presentation of parkinsonism, whereas in LBD, cognitive impairment often precedes parkinsonism (Aarsland, 2016). In idiopathic PD, cognitive impairment ranges from subjective cognitive decline, to mild cognitive impairment (MCI), to dementia, but does not necessarily progress linearly.

Longitudinal studies suggest MCI in PD increases the risk of developing Parkinson's disease dementia (PDD). Janvin et al., showed, whilst controlling for age, disease stage, education, and gender, that MCI was strongly associated with PDD development (odds ratio 5.1; 95% CI, 1.51 to 16.24, $p=0.005$) over a four-year follow up (Janvin, 2006). However, this study included relatively small numbers. More recently, evidence suggests MCI may not always progress to PDD, with some patients remaining stable on longitudinal assessments or even reverting back to normal cognition (Lawson, 2017). The prevalence of MCI in PD ranges from 15-53% (Yarnall, 2013) but this large variation in prevalence is likely caused by differences in study settings (hospital versus community patients), variable clinical characteristics, and inconsistent definitions of MCI in PD. The Movement Disorders Society published a unifying set of diagnostic measures in 2012 to standardize practice across clinical trials (Litvan, 2011). From a clinical perspective, MCI and PDD can be best differentiated by determining whether the cognitive impairment significantly impacts activities of daily living.

Several longitudinal studies have demonstrated that approximately 50% of patients develop PDD ten years after initial PD diagnosis (Auyeung, 2012; Williams-Gray, 2013). The Sydney

Multicenter Study, the largest follow-up study of newly diagnosed patients, showed 83% of patients with PD developed PDD at 20 years post diagnosis and 75% developed PDD before death (Hely, 2008). Additionally, not only does the progression of cognitive impairment in PD vary, so too does the pattern of cognitive deficits. Cognitive deficits may affect executive function, attention, processing speed and/or visuospatial function (Williams-Gray, 2007). The CamPaIGN (Cambridgeshire Parkinson's Incidence from GP to Neurologist) cohort study assessed cognition at 3.5 and 5.5 years post diagnosis and found a decline in MMSE (mini-mental state examination) score at a rate of 0.3 ± 0.1 points per year over 5.2 years (Williams-Gray, 2009). In addition, they showed that deficits in semantic fluency and visuospatial function at baseline were associated with a greater risk for developing PDD whereas deficits in executive function were not (Williams-Gray, 2007, 2009). This finding, in addition to other studies, led to the "dual syndrome hypothesis" which suggests that patients with primarily executive dysfunction, driven by changes in dopaminergic pathways, are less likely to develop PDD, whereas those with memory and visuospatial functional deficits, caused predominantly by deficits in acetylcholine, are more prone to rapid cognitive decline and progression to PDD.

The heterogeneity of both the presentation and progression of cognitive impairment in PD is not fully understood and is clearly a complex interplay between genetic and environmental factors. Risk factors associated with an increased risk for PDD include patient age, older age of disease onset, and the presence of hallucinations. In addition, the Parkinson's phenotype with more predominant gait dysfunction are associated with a more rapid cognitive decline than those with a tremor dominant phenotype (Williams-Gray, 2009). Genetic factors also play a role with mutations in the alpha-synuclein gene (*SCNA*) mutation (Waxman, 2009) and glucocerebrosidase (*GBA -1*) gene (Cilia, 2016) being associated with a more rapid cognitive decline, in addition to an earlier onset of PDD. One retrospective longitudinal study found that that 56% of *GBA1* mutation carriers had dementia at age 70, compared with 15% of sporadic PD patients (Cilia, 2016). Interestingly, patients with a *PARKIN* mutation, which accounts for 50% of autosomal recessive PD, are less likely to develop PDD, with one review finding PDD in fewer than 3% of cases (Grünewald, 2013).

The only drug currently licensed for PDD is rivastigmine, an acetyl cholinesterase inhibitor, with Memantine, an N-methyl-D-Aspartate (NMDA) receptor antagonist used as second line if the patient is intolerant to Rivastigmine (National Institute for Health and Care Excellence, 2017). However, a meta-analysis including three randomized controlled trials comparing memantine 20mg daily to placebo concluded it only had a mildly beneficial effect on the global impression of change assessment, with no significant change on cognitive function assessed using the MMSE (Wang, 2015). There is currently no successful treatment for MCI, and given the limited pharmacological options, it is important to consider non-pharmacological options including physical exercise programmes, cognitive training and stimulation using pharmacological and non-pharmacological approaches.

A systematic review of eight studies including 158 patients suggested that physical exercise had beneficial effects on global cognition, in particular on executive function, as assessed using the MoCA scale (Cruise, 2011; Murray, 2014). Physical activity intervention studies have historically recruited small numbers of patients and utilized heterogeneous interventions with varying degrees of exercise intensity, mode and duration.

Cognitive training is a structured teaching programme designed to target specific cognitive domains. A meta-analysis involving seven studies (n=272 patients) showed a small but statistically significant improvement compared with controls (Leung, 2015). Overall, given the heterogeneity of cognitive impairment in PD and the impact it has on the patient's quality of life and carer burden, the primary aim of management should be to apply an individualised approach whilst addressing patient and carer concerns and expectations.

Delirium

Given the propensity to develop dementia and the high degree of cognitive vulnerability it is proposed that people with PD are at increased risk of developing delirium in the setting of acute illness (Vardy, 2015). The features of delirium such as cognitive fluctuation, somnolence, and hallucinations can overlap with those seen particularly in PDD which can confound the diagnosis. There is a lack of evidence as to the long-term motor and cognitive outcomes for people with PD who have experienced delirium although there is a suggestion that both domains can worsen, albeit the studies were relatively small (Serrano-Dueñas,

2005; Umemura, 2014). Whilst antipsychotics can worsen motor symptoms, clinically quetiapine is most commonly used where pharmacological strategies are required in addition to treating any underlying precipitants and using conservative strategies such as one-to-one nursing and environmental optimisation.

Treatment related disorders

Impulse control disorders

Impulse control disorders (ICDs) are addictive behaviours manifesting as binge eating, pathological gambling, compulsive shopping, or abnormal sexual behaviours (Weintraub, 2010). These can occur in isolation or together. In Parkinson's disease they are associated with dopamine agonist therapy, and all patients initiated on this treatment should be counselled as to the risk and proactive enquiry at subsequent appointments should be used to ascertain whether these symptoms are arising. Left unrecognized and untreated, ICDs can have very significant ramifications on personal relationships and finances. Individuals at higher risk of developing ICDs are men, those with certain personality traits or psychiatric disturbance (such as impulsivity, novelty-seeking, anxiety, and depression), younger patients, smokers, and those taking higher doses of DA (dopamine agonists) for a longer duration. Management consists of down-titration of DA therapy supported by cognitive behavioural therapy with careful management of worsening motor symptoms (Okai, 2013).

Dopamine agonist withdrawal (DAWS)

Dopamine agonist withdrawal results from the rapid down titration or withdrawal of a dopamine agonist drug. Clinically is recognized by a cluster of symptoms including autonomic instability (fatigue, orthostatic hypotension, nausea, vomiting, diaphoresis), psychological symptoms (anxiety, panic attacks, dysphoria, depression, fatigue, agitation, irritability, suicidal ideation) as well as generalised pain, and drug cravings (Nirenberg, 2013). [67] The cessation or rapid reduction of dopamine agonist drugs is a major factor in the development of the syndrome and patients should be monitored closely in case this occurs.

Dopamine dysregulation syndrome (DDS)

Dopamine dysregulation syndrome refers to the compulsive (mis)use of dopaminergic therapy. The combination of dopamine replacement therapy, coupled with predisposing individual risk factors and PD pathology, yielding an addictive syndrome (Béreau, 2018). This manifests as mood fluctuations and addictive behaviour. Management consists of careful down titration of dopamine agonist therapy and fractionation of levodopa therapy. Intrajejunal levodopa infusion therapy or deep brain stimulation can be considered in refractory cases.

Conclusion

Neuropsychiatric manifestations of PD are common and have a devastating effect on patients' quality of life and cause significant carer strain. Assessment and active management of the neuropsychiatric symptoms encountered in people with PD is essential to mitigate these very distressing sequelae and the resultant negative impact these conditions can have on functioning. The overlap of symptoms can make the diagnosis of a mental health disorder in the context of PD challenging, but proactive enquiry is the first step in better defining and treating these syndromes. In this brief review we have sought to give an overview of the spectrum of conditions, current understanding of pathophysiology, criteria for diagnosis, and management strategies.

References

- Aarsland, D (2016) *Cognitive impairment in Parkinson's disease and dementia with Lewy bodies*, *Parkinsonism and Related Disorders*, 22: S144–S148.
- Aarsland, D, Brønnick, K, Alves, G, *et al* (2009) *The spectrum of neuropsychiatric symptoms in patients with early untreated Parkinson's disease*, *Journal of Neurology, Neurosurgery and Psychiatry*, 80(8): 928–930.
- Aarsland, D, Larsen, J, Tandberg, E, *et al* (2000) *Predictors of nursing home placement in Parkinson's disease: A population-based, prospective study*, *Journal of the American Geriatrics Society*, 48(8): 938–942.
- Aarsland, D, Larsen, JP, Karlsen, K, *et al* (1999) *Mental symptoms in Parkinson's disease are important contributors to caregiver distress*, *International Journal of Geriatric Psychiatry*, 14(10): 866–874.
- Aarsland, D, Marsh, L and Schrag, A (2009) *Neuropsychiatric symptoms in Parkinson's disease*, *Movement Disorders*, 24(15): 2175–2186.
- Auyeung, M, Tsoi, T, Mok, V, *et al* (2012) *Ten year survival and outcomes in a prospective cohort of new onset Chinese Parkinson's disease patients*, *Journal of Neurology, Neurosurgery and Psychiatry*, 83(6): 607–611.
- Barone, P, Poewe, W, Albrecht, S, *et al* (2010) *Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial*, *The Lancet Neurology*, 9(6): 573–580.
- Béreau, M, Fleury, V, Bouthour, W, *et al* (2018) *Hyperdopaminergic behavioral spectrum in Parkinson's disease: A review*, *Revue Neurologique*, 174(9): 653–663.
- Broen, MPG, Narayan, NE, Kuijf, ML, *et al* (2016) *Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis*, *Movement Disorders*, 31(8): 1125–1133.
- den Brok, MGHE, van Dalen, JW, van Gool, WA, *et al* (2015) *Apathy in Parkinson's disease: A systematic review and meta-analysis*, *Movement Disorders*, 30(6): 759–769.

Burn, D, Emre, M, McKeith, I, *et al* (2006) *Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease*, *Movement Disorders*, 21(11): 1899–1907.

Carlson, JM, Foti, D, Mujica-Parodi, LR, *et al* (2011) *Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: A combined ERP and fMRI study*, *NeuroImage*, 57(4): 1608–1616.

Carrozzino, D (2019) *Clinimetric approach to rating scales for the assessment of apathy in Parkinson's disease: A systematic review*, *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 94(April): 109641.

Chaudhuri, KR, Martinez-Martin, P, Antonini, A, *et al* (2013) *Rotigotine and specific non-motor symptoms of Parkinson's disease: Post hoc analysis of RECOVER*, *Parkinsonism and Related Disorders*, 19(7): 660–665.

Cilia, R, Tunesi, S, Marotta, G, *et al* (2016) *Survival and dementia in GBA-associated Parkinson's disease: The mutation matters*, *Annals of Neurology*, 80(5): 662–673.

Cruise, KE, Bucks, RS, Loftus, AM, *et al* (2011) *Exercise and Parkinson's: Benefits for cognition and quality of life*, *Acta Neurologica Scandinavica*, 123(1): 13–19.

Cummings, J, Isaacson, S, Mills, R, *et al* (2014) *Pimavanserin for patients with Parkinson's disease psychosis: A randomised, placebo-controlled phase 3 trial*, *The Lancet*, 383(9916): 533–540.

Devos, D, Moreau, C, Maltête, D, *et al* (2014) *Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: A double-blind, placebo-controlled, randomised clinical trial*, *Journal of Neurology, Neurosurgery and Psychiatry*, 85(6): 668–674.

Dissanayaka, NNW, Sellbach, A, Matheson, S, *et al* (2010) *Anxiety disorders in Parkinson's disease: Prevalence and risk factors*, *Movement Disorders*, 25(7): 838–845.

Dissanayaka, NNW, Sellbach, A, Silburn, PA, *et al* (2011) *Factors associated with depression in Parkinson's disease*, *Journal of Affective Disorders*, 132(1–2): 82–88.

Findley, L, Eichhorn, T, Janca, A, *et al* (2002) *Factors impacting on quality of life in Parkinson's*

disease: Results from an international survey, *Movement Disorders*, 60–67.

Forsaa, EB, Larsen, JP, Wentzel-Larsen, T, *et al* (2010) *A 12-year population-based study of psychosis in Parkinson disease*, *Archives of Neurology*, 67(8): 996–1001.

Gibson, G, Mottram, PG, Burn, DJ, *et al* (2013) *Frequency, prevalence, incidence and risk factors associated with visual hallucinations in a sample of patients with Parkinson's disease: a longitudinal 4-year study.*, *International journal of geriatric psychiatry*, 28(6): 626–31.

Grünewald, A, Kasten, M, Ziegler, A, *et al* (2013) *Next-generation phenotyping using the Parkin example: Time to catch up with genetics*, *JAMA Neurology*, 70(9): 1186–1191.

Hely, MA, Reid, WGJ, Adena, MA, *et al* (2008) *The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years.*, *Movement Disorders*, 23(6): 837–44.

Huse, D, Schulman, K, Orsini, L, *et al* (2005) *Factors impacting on quality of life in Parkinson's disease: results from an international survey.*, *Movement disorders*, 20(11): 1449–1454.

Janvin, CC, Larsen, JP, Aarsland, D, *et al* (2006) *Subtypes of mild cognitive impairment in Parkinson's disease: Progression to dementia*, *Movement Disorders*, 21(9): 1343–1349.

Klingelhoefer, L and Reichmann, H (2015) *Pathogenesis of Parkinson disease - The gut-brain axis and environmental factors*, *Nature Reviews Neurology*, 11(11) 625–636.

Koychev, I and Okai, D (2017) *Cognitive-behavioural therapy for non-motor symptoms of Parkinson's disease: A clinical review*, *Evidence-Based Mental Health*, 20(1): 15–20.

Lawson, RA, Yarnall, AJ, Duncan, GW, *et al* (2017) *Stability of mild cognitive impairment in newly diagnosed Parkinson's disease*, *Journal of Neurology, Neurosurgery and Psychiatry*, 88(8): 648–652.

Leentjens, AFG, Dujardin, K, Marsh, L, *et al* (2008) *Anxiety rating scales in Parkinson's disease: Critique and recommendations*, *Movement Disorders*, 23(14): 2015–2025.

Leung, IH, Walton, CC, Hallock, H, *et al* (2015) *Cognitive training in Parkinson disease A systematic review and meta-analysis*. *Neurology*, 85(21): 1843-1851.

Levy, G, Tang, M-X, Louis, ED, *et al* (2002) *The association of incident dementia with mortality in PD.*, *Neurology*, 59(11): 1708–13.

- Litvan, I, Aarsland, D, Adler, CH, *et al* (2011) *MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI.*, *Movement Disorders*, 26(10): 1814–24.
- Marin, RS (1991) *Apathy: A neuropsychiatric syndrome*, *Journal of Neuropsychiatry and Clinical Neurosciences*, 3(3): 243–254.
- Marsh, L, McDonald, WM, Cummings, J, *et al* (2006) *Provisional diagnostic criteria for depression in Parkinson's disease: Report of an NINDS/NIMH Work Group*, *Movement Disorders*, 21(2): 148–158.
- Marsh, L, Williams, JR, Rocco, M, *et al* (2004) *Psychiatric comorbidities in patients with Parkinson disease and psychosis.* *Neurology*, 63(2): 293-300.
- Menza, MA, Sage, J, Marshall, E, *et al* (1990) *Mood changes and 'on-off' phenomena in Parkinson's disease*, *Movement Disorders*, 5(2): 148–151.
- Murray, DK, Sacheli, MA, Eng, JJ, *et al* (2014) *The effects of exercise on cognition in Parkinson's disease: A systematic review*, *Translational Neurodegeneration*. 3(1): 5.
- National Institute for Health and Care Excellence (2017) *Parkinson's disease in adults. NICE guideline (NG71).*, NICE Guidelines, (July 2017).
- Nirenberg, MJ (2013) *Dopamine agonist withdrawal syndrome: Implications for patient care*, *Drugs and Aging*, 30(8): 587–592.
- Okai, D, Askey-Jones, S, Samuel, M, *et al* (2013) *Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers.* *Neurology*, 80(9): 792-799.
- Pagonabarraga, J, Kulisevsky, J, Strafella, AP, *et al* (2015a) *Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment*, *The Lancet Neurology*, 14(5): 518–531.
- Pagonabarraga, J, Kulisevsky, J, Strafella, AP, *et al* (2015b) *Apathy in Parkinson's disease: Clinical features, neural substrates, diagnosis, and treatment*, *The Lancet Neurology*, 14(5): 518–531.
- Parkinson, J, 1817. *An Essay on the Shaking Palsy* (London: Sherwood, Neely and Jones).
- Perepezko, K, Hinkle, JT, Shepard, MD, *et al* (2019) *Social role functioning in Parkinson's disease: A mixed-methods systematic review*, *International Journal of Geriatric Psychiatry*, 1128–1138.
- Pontone, GM, Williams, JR, Anderson, KE, *et al* (2009) *Prevalence of anxiety disorders and anxiety*

- subtypes in patients with Parkinson's disease*, *Movement Disorders*, 24(9): 1333–1338.
- Prediger, RDS, Matheus, FC, Schwarzbald, ML, *et al* (2012) *Anxiety in Parkinson's disease: a critical review of experimental and clinical studies.*, *Neuropharmacology*, 62(1): 115–24.
- Ravina, B, Marder, K, Fernandez, HH, *et al* (2007) *Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group.*, *Movement Disorders*, 22(8): 1061–8.
- Reijnders, JSAM, Ehrt, U, Weber, WEJ, *et al* (2008) *A systematic review of prevalence studies of depression in Parkinson's disease*, *Movement Disorders*, 23(2): 183–189.
- Richard, IH, Kurlan, R, Tanner, C, *et al* (1997) *Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group.*, *Neurology*, 48(4): 1070–7.
- Riedel, O, Klotsche, J, Spottke, A, *et al* (2010) *Frequency of dementia, depression, and other neuropsychiatric symptoms in 1,449 outpatients with Parkinson's disease*, *Journal of Neurology*, 257(7): 1073–1082.
- Serrano-Dueñas, M and Bleda, MJ (2005) *Delirium in Parkinson's disease patients. A five-year follow-up study*, *Parkinsonism and Related Disorders*, 11(6): 387–392.
- Shulman, LM, Armstrong, M, Ellis, T, *et al* (2016) *Disability Rating Scales in Parkinson's Disease: Critique and Recommendations*, *Movement Disorders*, 31(10): 1455–1465.
- Shulman, LM, Taback, RL, Rabinstein, AA, *et al* (2002) *Non-recognition of depression and other non-motor symptoms in Parkinson's disease*, *Parkinsonism and Related Disorders*, 8(3): 193–197.
- Umemura, A, Oeda, T, Tomita, S, *et al* (2014) *Delirium and high fever are associated with subacute motor deterioration in parkinson disease: A nested case-control study*, *PLoS ONE*, 9(6).
- Vardy, ERLC, Teodorczuk, A and Yarnall, AJ (2015) *Review of delirium in patients with Parkinson's disease*, *Journal of Neurology*, 262(11): 2401–2410.
- van der Velden, RMJ, Broen, MPG, Kuijf, ML, *et al* (2018) *Frequency of mood and anxiety fluctuations in Parkinson's disease patients with motor fluctuations: A systematic review*, *Movement Disorders*, 33(10): 1521–1527.
- Wang, HF, Yu, JT, Tang, SW, *et al* (2015) *Efficacy and safety of cholinesterase inhibitors and*

memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: Systematic review with meta-analysis and trial sequential analysis, Journal of Neurology, Neurosurgery and Psychiatry, 86(2): 135–143.

Waxman, EA and Giasson, BI (2009) *Molecular mechanisms of α -synuclein neurodegeneration*, Biochimica et Biophysica Acta - Molecular Basis of Disease, 1792(7): 616–624.

Weintraub, D and Burn, DJ (2011) *Parkinson's disease: the quintessential neuropsychiatric disorder.*, Movement Disorders, 26(6): 1022–31.

Weintraub, D, Koester, J, Potenza, MN, et al (2010) *Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients*, Archives of Neurology, 67(5): 589–595.

Williams-Gray, CH, Evans, JR, Goris, A, et al (2009) *The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort*, Brain, 132(11): 2958–2969.

Williams-Gray, CH, Foltynie, T, Brayne, CEG, et al (2007) *Evolution of cognitive dysfunction in an incident Parkinson's disease cohort*, Brain, 130(7): 1787–1798.

Williams-Gray, CH, Mason, SL, Evans, JR, et al (2013) *The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort*, Journal of Neurology, Neurosurgery and Psychiatry, 84(11): 1258–1264.

Yarnall, AJ, Rochester, L and Burn, DJ (2013) *Mild cognitive impairment in Parkinson's disease.*, Age and ageing, 42(5): 567–76.

Learning Objectives:

- By the end of the manuscript the reader will
- understand the scope of the potential psychiatric manifestations of Parkinson's disease, including those which may be caused by or precipitated by treatments.
- recognise assessment scales that are available to aid diagnoses of neuropsychiatric conditions.
- Have insight into some of the current treatments for the mental health problems that are encountered in people with Parkinson's and the areas in which a strong evidence base is lacking.

MCQ's

Select the single best answer for each question stem

1. When considering depression in Parkinson's disease:
 - a) there is no relationship between rates of depression and severity of motor symptoms
 - b) Validated screening tools include Hospital Apathy and Depression scale (HADS), Starkstein Apathy Scale (SAS) and Geriatric Depression Scale (GDS)
 - c) Motor "on" or "off" state should be considered when making a diagnosis of depression
 - d) Dopamine Agonists should be avoided in patients with depression
 - e) Serotonin syndrome is commonly clinically encountered in patients with PD depression

2. Impulse control disorders are most commonly associated with:
 - a) Levodopa
 - b) Dopamine agonists
 - c) Monoamine oxidase inhibitors
 - d) Catechol-O-methyltransferase (COMT) inhibitors
 - e) Deep brain stimulation

3. With regards to Anxiety:
 - a) Obsessive compulsive disorder is the commonest disorder seen in patients with PD
 - b) There are no gold standard diagnostic criteria
 - c) A longer serotonin transporter allele is associated with higher levels of anxiety in PD
 - d) Medical causes should be excluded before diagnosing an anxiety disorder
 - e) Benzodiazepines are the first line in treatment of anxiety in PD

4. Patients with PD:
 - a) are more likely to develop rapid cognitive decline if they are of tremor-dominant phenotype
 - b) are more likely to develop PD dementia if they possess the PARKIN mutation
 - c) Should be offered memantine as first line therapy

- d) Are unlikely to benefit from physical therapy with regards to their cognition
- e) Who have visuospatial dysfunction, are more likely to develop PD dementia

5. With regards to psychosis in PD:

- a) Psychosis exclusively presents late in the course of PD
- b) Quetiapine and risperidone do not affect motor symptoms
- c) Prevalence increases with disease duration
- d) Treatment of psychotic symptoms should be initiated regardless of the impact the symptoms are having on the patient.
- e) There is strong evidence of association between PD medication and psychosis

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SJ wrote the first draft with support from KT. LS contributed to the section on anxiety and KB to the background review and figures. EJM supervised the writing and all authors approved the final manuscript.