Therapy in Practice: Assessment and Management of Neuropsychiatric Symptoms in Parkinson's Disease

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Compliance with ethical standards

Declarations of interest:

K.R.C. has consulted and served on advisory boards for Britannia, AbbVie, Neuronova, Mundipharma and UCB, and has also served on advisory boards for Synapsus and Medtronic. He has received honoraria from Boehringer Ingelheim, GlaxoSmithKline, AbbVie, Britannia, UCB, Mundipharma, Otsuka and Zambon, and grants from Boehringer Ingelheim, GlaxoSmithKline, Britannia, AbbVie, UCB and Neuronova. He holds intellectual property rights for the KPP scale and the PDSS, and receives royalties for the books Non-Motor Symptoms of Parkinson's Disease and Fastfacts: Parkinson's Disease. D.A. has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals, GE Health, Easi, Heptares and serves as a paid consultant for H. Lundbeck and Axovant. CM, APR, WYM, LV and Dff declare no competing interests.

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Abstract (195/250)

Neuropsychiatric symptoms are highly prevalent in Parkinson's disease and associated with decreased quality of life and adverse health outcomes. In this review the assessment and management of common neuropsychiatric symptoms are discussed: depression, anxiety, psychosis, cognitive impairment, dementia and apathy. Validated assessment scales are now available for the majority of symptoms. Balancing dopaminergic therapy plays an important role in their management as increasing doses of dopaminergic agents might address depression and anxiety related to 'off' phases, nonmotor fluctuations and apathy, while dose reduction might alleviate psychotic symptoms. More targeted treatment is possible through medications utilizing different pathways. Although efficacy profiles of individual agents require further exploration, antidepressants as a drug class have shown utility in depression and anxiety in Parkinson's disease. Psychological therapies, especially cognitive behavioral approaches, are effective. pimavanserin allows treatment of psychosis in Parkinson's disease without directly affecting the dopaminergic and cholinergic system. The cholinergic system is currently the only target in in Parkinson's disease dementia, and antagonists of this system, as are many psychotropics, need to be used with caution. Management of apathy largely relies on non-pharmacological strategies adapted from dementia care, with antidepressants being ineffective and the role of stimulant therapy needing further evaluation.

Key points: 3-4 sentences

- Neuropsychiatric are closely interwoven with motor symptoms and nonmotor fluctuations, making differentiation challenging, and leading to underdiagnoses and underreporting.

- The increasing availability of validated, easy-to-use, screening tools might allow earlier recognition in clinical practice.

- Adjustment of dopaminergic therapy plays an important role and dopaminergic agonists with the potential to simultaneously address motor and non-motor symptoms such as depression or apathy have shown promising potential.

- There is acceptable evidence for acetylcholinesterase inhibitors (dementia), clozapine (hallucinations), and antidepressants.

1. Introduction

Neuropsychiatric symptoms are common already at the time of diagnosis of Parkinson's disease (PD) [1] and in more advanced stages their impact is often greater than that of motor symptoms. The most frequent symptoms are depression, hallucinations and apathy and many patients have more than one symptom, adding to the complexity and challenge both for patients and for their caregivers [2]. Neuropsychiatric symptoms are strong predictors of poor quality of life and key drivers for nursing home admission and thus are costly for society. This review gives an overview on clinical presentation, diagnostic tools and management strategies for neuropsychiatric symptoms in PD. The electronic database PubMed Medline was searched with the search terms "Parkinson OR Parkinson's disease OR PD" and "neuropsychiatric OR depression OR anxiety OR fatigue OR apathy OR cognition OR cognitive decline OR dementia OR psychosis OR hallucination OR apathy OR fatigue". Cross-references from the identified articles were also scrutinised for relevant studies. Articles were selected through authors consensus with a focus on studies evaluating treatment interventions as well as recent state-of-the-art review articles. Assessment instruments for individual symptoms are described in the relevant subsections below, but an initial screening can be conducted using scales covering multiple symptoms. Instruments covering several symptoms include the Neuropsychiatric Inventory (NPI) [3], or the Non-Motor Symptoms Scale for Parkinson's disease (NMSS) [4]. Of note, the revised Movement Disorder Society (MDS) version of the Unified Parkinson Disease Rating Scale (UPDRS) has an increased focus on neuropsychiatric symptoms [5], demonstrating the increased acknowledgement of the relevance of these symptoms as part of the core syndrome.

2. Depression

Depression in PD is associated with increased caregiver burden and mortality, as well as decreased functioning, quality of life and possibly cognitive decline [6, 7]. Although the prevalence rates vary considerably according to sample definitions and assessment criteria, about one third [8] of patients with PD are considered to suffer from clinically relevant depressive symptoms. A family history of depression and previous depressive episodes, as well as female gender, early onset of PD and other neuropsychiatric symptoms have been identified as possible risk factors for depression in PD [9]. Neurobiological factors that might play a role are degeneration in the serotonergic raphe nucleus and noradrenergic locus coeruleus as well as dysregulation of the dopaminergic circuits in the frontostriatal and mesolimbic regions [10].

2.1 Assessment

Low mood, reduced energy and capacity for enjoyment (anhedonia) are the core symptoms of depression. Other features include disturbed sleep, changes in appetite and weight, impaired concentration, slowness of thinking and movement and a blunted affect. However, many of these can overlap with symptoms of PD, in particular in the advanced stages, making the distinction between the two difficult [11].

Clinically it can be helpful to consider fatigability of movement in PD in contrast to general slowness in depression, impaired concentration in depression compared to a more generalized cognitive impairment pointing towards dementia in PD and the longitudinal course of sleep disturbances, whereby a more recent onset might indicate depression [12]. Negative cognitions, such as guilt or worthlessness are less common in depression in Parkinson's disease [13]. In clinical settings diagnosis of depression should be made according to the International Classification of Disease version ten (ICD-10) [14] or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [15] criteria, and screening tools can be useful. Although suicidality is less common in patients with PD than in the general population this should always be assessed.

An additional challenge specific to PD is the differentiating depression from non-motor fluctuations, fatigue, apathy (see Chapter 6) or dementia (see Chapter 5).

Non-motor fluctuations are related to wearing-off of dopaminergic therapy and can present as low mood, anxiety, apathy or fatigue. They are might present in the absence of motor fluctuations and often difficult to diagnose in clinical practice [16]. Several assessment tools have been developed (such as the Non-Motor Fluctuation Assessment [17] or the 19-item Wearing-OFF Questionnaire as screening tool [18]) for research settings. In routine clinical settings it is crucial to establish whether neuropsychiatric symptoms improve after the patient has administered a dopaminergic agonist.

Fatigue is a diagnostic criterion for depression or anxiety [15], but can also be a primary feature of PD [19]. Evidence on successful treatment strategies of primary fatigue in Parkinson's disease is missing [20] and the use of antidepressants cannot be recommend in the treatment of fatigue, unless a diagnosis of depression according to established criteria is present. Although it is important to identify fatigue as part of a depressive syndrome, a considerable number of patients will complain about unresolved fatigue after successful treatment of depressive symptoms [21].

The last potential diagnostic pitfall is distinguishing dementia in PD from depression, as the cognitive profile of late-life depression, with characteristic difficulties in attentional and executive domains, is very similar to dementia in PD [22, 23]. Pointers towards a diagnosis of depression rather than dementia might be a subacute onset of symptoms over days to weeks rather than months, a mismatch between functional impairment and cognitive test scores, greater awareness of cognitive deficits, saying 'I don't know' rather than confabulating answers in testing, as well as preserved visuospatial abilities [23-25]. In uncertain cases, use of in-depth neuropsychological testing or use of biomarkers on cognitive decline (see Chapter 5) should be considered.

A recent meta-analysis [26] identified three tools to be specific and sensitive for detecting depression in PD: the 15-item Geriatric Depression Scale (GDS-15), Beck Depression Inventory (BDI-I or Ia); Montgomery-Åsberg Depression Rating Scale (MADRS). Not enough data is available to conduct a meta-analyse of psychometric properties related to detecting depression for instruments such as the Hamilton Depression Rating Scale (HAM-D), the Hospital Anxiety and Depression Scale (HADS) and the Zung Self-Rating Depression Scale

(SDS). These were they were included in a critique by a taskforce of the Movement Disorders Society, which also provides adjusted cut-off scores compared to those in non-PD populations [27].

The GDS-15 [28] is an ideal screening tool as it is available in the public domain, translated into several languages and quick to administer. The GDS-15 is a self-rated tool which takes 5-10 minutes to administer, asking yes/no questions. Its focus on cognitive and social aspects of depression, rather than somatic concerns, and reduces the impact of motor symptoms on the overall score. A cut-off of 5 appears to be appropriate as this yields a sensitivity of 91% [26].

The BDI [29], HAM-D [30] (Hamilton, 1960) and MADRS [31] can be used both as screening tools, but also to measure change over time.
The BDI is self-rated and takes 5-10 minutes to administer and the HAM-D and MADRS are clinician rated and take 10-15 and 15-20 minutes to administer. The HAM-D is the most frequently administered tool in clinical trials to measure efficacy and has been classified as most suitable for assessing depression severity in research settings [27].

If time-pressures in clinical practice do not allow the regular use of structured tools, focus should be on detecting depression using a short screening tool as GDS-15. In general hospital settings and primary care, the UK National Institute for Health and Care Excellence (NICE) [32] recommends the use of a two-question screen to detect depression, asking two 'yes/no' questions: 'During the last month, have you often been bothered by feeling down, depressed or hopeless?' and 'During the last month, have you often been bothered by having little interest or pleasure in doing things?'. A recent meta-analysis found that this tool had a sensitivity of 92% and a specificity of 68% in older adults and its performance is comparable with other instruments in this population [33]. Although this needs formal validation in PD, it might be a useful and cost-effective approach to screen for depression in this population.

2.2 Management

A holistic approach is essential in the management of depression in PD. Assessment tools and a treatment algorithm are illustrated in Figure 1. Organic causes (e.g. hypothyroidism) need to be excluded and if present addressed.

It is important to determine if depressive symptoms are only seen in 'off' periods or are due to non-motor fluctuations. In these circumstances adjustment of dopaminergic or other medications prescribed for motor symptoms can alleviate symptoms, and is more likely to be beneficial than depression-specific treatments [34]. Established strategies for the treatment of motor symptoms can be followed, but care should be taken in older patients, those with orthostatic hypotension and co-morbid other neuropsychiatric symptoms [11]. Adding pramipexole, a dopaminergic agonist with probable antidepressant properties [35], could be considered.

In milder cases guided self-help, psychoeducation, advice on exercise and sleep hygiene, support groups and/or involvement of the support network are often sufficient. Cognitive behaviour therapy (CBT) is the best evaluated non-pharmacological intervention [36, 37], showing good effects on depressive and secondary anxiety symptoms in PD, both administered individually or in group settings. Pachana and colleagues [7] argue that CBT needs to address factors specifically relevant to patients with PD such as beliefs about their illness and the impact of disability. Working with grief and loss (of functioning) are important [38], especially as these can ameliorate anxiety over the future and enable better coping with disability. A specific focus should be on regaining functioning that has been lost due to avoidance rather than inability. As PD is a neurodegenerative disease with progressive deterioration it is unclear if the benefits of psychological therapies are sustained after the intervention concludes. A further limiting factor for CBT interventions are practical obstacles to attending therapy, such as living in remote areas, lack of transportation or caregiver support, or fluctuations in motor symptoms [39]. There has been a recent effort to develop telehealth interventions, which have indicated feasibility and good retention rates, but require larger scale evaluation [40-45].

In moderate to severe depression, or where non-pharmacological measures haven't been successful, drug treatment should be considered. Antidepressant medication can further be

helpful in reducing symptoms to a level that enable patients to engage with psychological therapy.

Although their effect sizes are modest and not all clinical trials report superiority to placebo, due to their benign safety profile selective serotonin re-uptake inhibitors (SSRI) are considered first-line treatments [37]. Superiority to placebo in randomized clinical trials has been demonstrated for citalopram, paroxetine and the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine [46, 47]. Venlafaxine was not superior to paroxetine [47] and no advantage to placebo was reported in other trials for citalopram, paroxetine, as well as sertraline [37]. It has however been speculated that placebo responses might be exaggerated in PD due to the release of dopamine in anticipation of a therapeutic benefit [48, 49]. One needs to be aware of an increased risk of a serotonin syndrome when SSRIs and the MAO-B inhibitor selegeline are co-prescribed [50] and the SNRI venlafaxine has been associated with a worsening of motor symptoms [47].

The tricyclic antidepressants (TCAs) nortriptyline and desipramine (the active metabolite of imipramine) appear to have larger effect sizes compared to placebo than SSRIs and a more rapid onset of benefits [46, 51]. This is probably related to their effect on the adrenergic and dopaminergic system, as well as improvement of sleep [37]. These agents could be of benefit when a more rapid resolution of depressive symptoms is desired (e.g. low food or fluid intake, suicidal ideation, psychotic depression). The flipside of this is that TCAs are associated with adverse effects on the cardiovascular system and the propensity to worsen autonomic dysfunction, and should be used with caution in those with cardiovascular disorders, orthostatic hypotension, urinary retention and angle closure glaucoma [11]. Anticholinergic effects could improve motor symptoms, but they are likely to worsen psychotic symptoms and cognition (see Chapter 4). Practical considerations are that SSRIs/SNRIs should be given in the mornings and TCAs at night. While SSRIs are usually started at the therapeutic dose, SNRIs and TCAs require titration [11]. We recommend starting with an SSRI and considering venlafaxine or TCA if insufficient effect or side-effects occur. Antidepressant dosing should follow recommended schedules for treatment of major depressive disorder in the elderly (for example [52]).

The potential antidepressant role of dopamine agonists, in particular pramipexole, has been of interest due to the possibility of addressing both motor and non-motor symptoms with a single

agent. Larger scale observational studies [53, 54] have shown beneficial effects of pramipexole specifically on anhedonia in PD depression, and a small head-to-head trial equivalent efficacy to sertraline [55]. One large double-blind placebo controlled RCT in patients with mild to moderate depression [35] showed small, but statistically significant, benefits of pramipexole compared to placebo. Groups who might benefit from pramipexole as first line treatment for PD depression are those who were recently diagnosed patients with PD suffering from mood symptoms, but have not been started on dopaminergic therapy; when symptoms occurred after a reduction in dopaminergic therapy; or when non-motor fluctuations could be the main driver of depressive symptoms [56, 57].

In other clinical contexts, treating motor and depressive symptoms with separate agents, and only using dopaminergic agents as second line treatments, might allow a more personalised approach [56].

Adverse effects of dopaminergic agents also need to be considered as well as the increased risk of psychosis (see Chapter 4) and impulse control disorders [58]. Pramipexole should be started on a low dose and titrated up over weeks, as an acute challenge can lead to worsening of mood and motivation [59].

Repetitive transcranial magnetic stimulation (rTMS) for depression led to improvement of symptoms, but these were not statistically significant compared to placebo treatment in two small studies [60, 61]. A more recent study of multifocal rTMS didn't show improvements of depressive symptoms and inferiority to sham treatment [62]. For life-threatening and treatment-resistant depression in Parkinson's disease electro-convulsive therapy (ECT) should be considered. No randomized controlled trials have been conducted using ECT in depression in PD, but case series and case reports have described benefits on depressive, psychotic (Chapter 4) as well as motor symptoms. A limiting factor is that the risk of delirium or transient confusion appears to substantial in this patient group, being reported in more than a third of patients treated [63].

3. Anxiety

Anxiety disorders are more common in patients with PD than in the general population or those with other chronic conditions [64], with about one third suffering from a diagnosable anxiety disorder [65].

Most common are generalised anxiety disorder (GAD), with the typical symptoms of persistent tension, irrational worrying and physical arousal; phobias, especially social phobias, and panic disorders [66].

3.1 Assessment

Compared to general populations, PD patients with anxiety more frequently suffer from internal tremor, as well as social or anticipatory anxiety [7, 65]. Common scales to assess anxiety, such as the Hospital Anxiety and Depression Scales (HADS), Hamilton Anxiety Rating Scale (HARS) and Beck Anxiety Inventory (BAI) are not appropriate to be used in PD [67]. Dissanayaka and colleagues [68] reviewed the literature on anxiety rating scales in PD and found that two scales have good validity and reliability: The Geriatric Anxiety Inventory (GAI) and the Parkinson's Anxiety scale (PAS).

The GAI is a 20-item self-report measure [69], using 'agree/disagree' responses, which takes about 10 minutes to administer. It focuses on cognitive symptoms of anxiety and less on somatic symptoms making it appropriate for use in PD [70]; a cut-off of 7 suggests an anxiety disorder. The PAS is a newly developed scale [71] and is a 12-item self- or observer-rated tool. Items are scored on a 5-point Likert scale, whereby 0 = 'not or never' and 4 = 'severe or almost always'. The optimal cut-off point to detect anxiety is 14. The self-rated version takes 2 minutes to complete and the observer rating 5 minutes. Sensitivity to change in anxiety in PD has not yet been evaluated.

3.2 Management

As in depression, a comprehensive assessment is needed to rule out other potential causes for anxiety (e.g. metabolic causes) or substance use. In particular, it should be established if

anxiety is present in an 'off' phase or due to nonmotor fluctuations and can be ameliorated by adjusting dopaminergic medication.

CBT is a well-established treatment for anxiety disorders and likely to be efficacious in PD [7]. The majority of studies have shown reduction of anxiety in the context of depression in PD, but a recent small study focussing primarily on anxiety demonstrated benefits in a small study of 12 patients [66]. For milder cases self-help should be encouraged.

No controlled studies have been conducted for antidepressants in anxiety in PD, but secondary benefits are reported from antidepressant studies [9]. Case studies have suggested benefits for citalopram, sertraline and paroxetine [72], but no beneficial effects for secondary anxiety in depression were shown in a randomized controlled trial for paroxetine and venlafaxine [47]. For disabling cases or where the anxiety causes the patient severe distress short-term treatment with benzodiazepines can be initiated for up to four weeks. In addition to their potential to cause physical dependence, benzodiazepines affect cognition, alertness and gait in patients with PD increasing the risk of falls [73].

4. Psychosis

PD psychosis is a term used to describe the range of illusions, hallucinations and delusions occurring in PD and related disorders (see Table 1 for typical manifestations in PD) [for review see 74]. In early PD the symptoms are predominantly illusions (a real object misperceived as something else) including pareidolia, a specific subtype of illusion. Other early symptoms include passage hallucinations and presence hallucinations. A range of other visual disturbances including isolated diplopia and spatial misjudgement have also been recently described [75, 76]. These early symptoms are sometimes referred to collectively as minor hallucinations. As PD progresses, formed visual hallucinations occur, typically of people or animals [often insects or small animals, 77]. At this stage insight into the fact they are hallucinations is preserved or, if absent when the experiences first occur, patients can learn to recognise that the experiences are hallucinations. In later stages, insight becomes impaired so that the experiences may no longer be recognised as hallucinations. Other hallucination modalities may also occur, either as separate hallucinations or as multimodality hallucinations that may be seen and heard at the same time. These experiences may occur alongside false beliefs (delusions) that can be linked to the hallucinations (secondary delusions) or have unrelated themes such as infidelity or persecution. Themes involving identity are referred to collectively as misidentification delusions. The typical progression of PD psychosis is illustrated in Figure 2. The boundary between different stages is blurred, and mirrors that of cognitive decline with early symptoms occurring without detectible cognitive change, formed hallucinations occurring at the mild cognitive impairment (PD-MCI) stage and hallucinations without insight and misidentification delusions in the context of dementia in PD (PDD). The prevalence of PD psychosis increases with disease duration, with most patients eventually developing such symptoms. However, estimates vary depending on whether minor symptoms are included. In cross-sectional studies, typical rates of complex visual hallucinations range from 22%-38% and auditory hallucinations around half this value (0%-22%) [78]. Patients who present with PD psychosis early in the disease have accelerated cognitive decline and worse longer-term outcomes [74]. In particular, visual hallucinations are associated with the move from living independently into a care setting, irrespective of motor impairment or cognitive ability [79].

The underlying cause of PD psychosis is currently unclear. Early theories linked PD psychosis to the use of dopamine therapy and it remains the case that PD psychosis often starts after the

onset of dopamine therapy and may improve with dose reduction. However, evidence that PD psychosis can occur without the use of dopamine medication and a lack of relationship between medication dose and symptom severity shows the relationship is complex. Current consensus on the role of dopamine therapy [see 80] is that PD psychosis may be integral to PD itself but triggered or modified by the use of dopamine medication. A reduction in striatal dopamine binding in PD prior to the onset of PD-Psychosis supports this view [81]. Other suggested pathophysiological mechanisms for PD psychosis include alterations in serotonergic function [82] and, based on evidence from DLB, alterations in cholinergic function [83]. There is also evidence for a specific profile of cognitive deficits in PD psychosis, including deficits in memory, executive function, visuo-spatial function and attention [for review see 74]. The cognitive changes are consistent with the distribution of cortical and hippocampal atrophy [for review see 74, 84]. PD psychosis is associated Lewy body, Tau and amyloid pathology [85] although whether the distribution or such pathology matches the distribution of cortical atrophy is unclear [74].

4.2 Assessment

Assessment of PD psychosis is carried out by clinical examination of the mental state, with information from a carer required in later stages of the disease. The stigma of visual hallucinations as a sign of mental illness may mean patients are reluctant to admit the symptoms in early stages so that direct and sensitive questioning is required. A range of quantitative assessment tools are used in research settings (Scale for the Assessment of Positive Symptoms – Parkinson's disease-adopted (SAPS-PD), North-East Visual Hallucinations Interview (NEVHI) and Neuropsychiatric Inventory (NPI)) but none cover the whole range of symptoms encountered in PD psychosis. There are no specific investigations for PD psychosis but where symptoms are atypical, further investigation may be required. For example, in a patient with visual hallucinations restricted to a portion of the visual field, detailed visual field testing, MRI of visual pathways and visual electrophysiology may be indicated.

4.3 Management

The management of PD psychosis differs across the disease course with the different treatment considerations for each stage illustrated in Figure 2. A key consideration throughout is the influence of dopamine therapy and the competing priorities of increasing dopamine therapy to optimise motor function and decreasing dopamine therapy to reduce PD psychosis symptoms. Other factors that require constant review are anti-muscarinic medication load [for example

using traffic-light coding of medication, 86], general physical health to rule out infection and delirium and optimisation of vision, for example through referral to ophthalmology. In early stages of disease, management by re-assurance, education and self-help strategies to stop hallucinations (for example, changes in lighting, eye movements or general alerting strategies) may be sufficient. For formed hallucinations that cause distress, psychological interventions to reduce general stress or designed specifically for visual hallucinations [87] may be helpful while insight is still present but as distress increases or insight is lost, medication may become the only option. Cholinesterase inhibitors, e.g. Rivastigmine may have a particularly good cognitive effect in people with hallucination in PD [88] but patients may already be on this medication for cognitive decline. Pimavanserin (a 5HT$_{2A}$ inverse agonist) has been recently approved for the treatment of PD psychosis and can be considered if available [89]. Clozapine is effective for PD psychosis but blood monitoring requirements may limit its practicality for some patients [90, 91]. Quetiapine is widely used because of its favourable extrapyramidal side-effect profile and has recommended in the 2017 [92]. However, clinical trial evidence to support a specific treatment role in PD psychosis is limited with several trials showing no effect over placebo [93-95]. Where treatment using these medications is ineffective or impractical, there is open label trial evidence to support the use of ECT [96, 97] or continuous subcutaneous apomorphine as an alternative to oral dopamine therapy [98] for PD psychosis [74].

Table 1 PD psychosis symptom phenomenology

SYMPTOM		TYPICAL MANIFESTATION IN PD
MINOR	Illusion	Brief misperception of one object for another.
	Pareidolia	Faces or animals triggered by visual context, for example by wallpaper / carpet patterns, tree bark or clouds. Pareidolia is a normal perceptual experience that increases in frequency in PD and DLB.
	Passage hallucination	A figure or person is seen moving past in the peripheral visual field and disappears on looking towards it.
	Presence hallucination	Sense of someone being next to you without seeing or hearing the person.
COMPLEX HALLUCINATION		Typically seeing a person or animal when not present. The person may be someone known. The experience may be recognised as a hallucination (insight present) or believed to be real (insight absent). Insight may also fluctuate or be partial such that the hallucination is recognised as having been false after the event but acted on as if real at the time it occurred.
PSEUDO-HALLUCINATION		Term used in the neurological literature to describe hallucinations with insight present. In psychiatric literature the term is used to describe vivid imagery (seen in mind's eye not external visual environment).
DELUSION		False belief typically of guilt, persecution or jealousy. If linked to a hallucination referred to as a secondary delusion (e.g. beliefs about the identify and intent of a hallucinated figure).
MISIDENTIFICATION DELUSION		Specific categories of false belief linked to identity. Capgras delusion is the belief that a relative has been replaced by an impostor. Reduplicative paramnesia is the belief that a specific location has been duplicated.

5. Cognitive decline and dementia

Cognitive decline is one of the most common non-motor symptoms in PD and people with PD have substantially increased risk of developing dementia compared to the general population. The point prevalence of dementia in people with PD is about 25-30% and the majority of patients with PD develop dementia if they survive 10 years or more from initial diagnosis [22]. Risk factors for a more rapid cognitive decline include more severe parkinsonism, especially bradykinesia and rigidity, higher age [99], the presence of visual hallucinations [100] and reduced Aβ42 levels in the cerebrospinal fluid [101]. Importantly, among PD patients without dementia 25-30% suffer from mild cognitive impairment [22].

Parkinson's disease dementia (PDD) and mild cognitive impairment in PD (PD-MCI) are operationalised as two separate entities, whereby the hallmark for PDD is that cognitive problems are sufficiently severe to impair activities of daily living independently of co-existing motor or autonomic symptoms [102, 103]. Up to one fifth [99] of patients present with PD-MCI at the stage of PD diagnosis, which is associated with a more rapid progression to dementia. However, a considerable proportion of these patients also revert back to normal cognition after one year [104].

The main pathological correlate of dementia in autopsy studies is the presence of cortical and limbic Lewy bodies (α-synucleinopathies) [105]. Other proteinopathies, with the evidence for amyloid plaques being more robust than for tau-pathology, contribute to the development of dementia and seem to have an additive influence [106, 107]. Both dopaminergic and non-dopaminergic transmitter deficits underlie cognitive decline and the cholinergic system appears to be affected early in the disease course of PD [108].

5.1 Assessment

Timely diagnosis of cognitive impairment and dementia in PD is important and operationalised diagnostic criteria exist [102, 103]. For a diagnosis of PDD [102] required core features are a diagnosis of PD and cognitive impairment in more than one domain, which is severe enough to impair activities of daily living. To make a diagnosis of probable, as opposed to possible, PDD a typical cognitive profile with impairment in at least two of the following domains needs

to be present: (I) attention (may fluctuate during the day or from day to day), (II) executive function, (III) visuo-spatial function and (IV) memory, in particular free recall, which usually improves with cueing.

Due to clinical and pathological overlap, the distinction of dementia in PD and dementia with DLB is challenging and the temporal sequence of symptoms is used to guide differential diagnosis. PDD develops in the context of established PD, and if dementia develops before or within one year of motor features of parkinsonism, DLB should be diagnosed. Although useful for research settings, the 1-year-rule is often difficult to apply in clinical practice since the exact timing of motor and cognitive symptoms may be difficult to establish [102]. However, this distinction is mainly of academic relevance, the clinical management is the same in PDD and DLB.

Although comprehensive neuropsychological testing is the gold standard, cognitive rating scales are useful in clinical practice for screening and monitoring. A Movement Disorder Society review committee recently made recommendations regarding the use of these tools [109]. The Montreal Cognitive Assessment battery (MoCA) [110], Mattis Dementia Rating Scale Second Edition (DRS-2) [111] (MD-11), and the Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [112] were endorsed. The most appropriate scale in clinical settings appears to be the MoCA as administration only takes around 10 minutes and it is sensitive to change over time [113]. Suggested cut-off points are for <26 PD-MCI and <21 for PDD [114]. Scales traditionally used in dementia services as the Mini-Mental State Examination (MMSE) [115] and Adenbrooks's Cognitive Examination (ACE-R) [116] were not recommended. The MMSE primarily tests cortical aspects of cognition, which are frequently preserved in PD, to the expense of inadequate testing of visuospatial and executive dysfunction [109]. The ACE-R [116] has good psychometric properties, but limited coverage of executive dysfunction [109]. Further, the new ACE-III [117] which has been introduced due to copyright issues, has not been evaluated in PD populations. Other non-motor symptoms which are common in PDD should also be recorded and global scales such as NPI [3] or NMSS [4] can be applied. All scales can be used as guidance, but need to be accompanied by clinical assessment of degree of functional cognitive decline, focusing on work-related functioning and for home-dwelling patients tasks such as managing medication regime, finances, computer and mobile phones.

CT or structural MRI have limited usefulness in terms of distinguishing PDD from other forms of dementia. Patients with PDD show greater atrophy of frontal, parietal, occipital and temporal cortices [22] and the severity of dementia correlates with medial temporal lobe atrophy [118]. PET imaging of glucose metabolism or Amyloid-β might allow clearer distinction of PDD from Alzheimer's disease, whereby amyloid-positive PET scans and reduced Aβ42 levels in the cerebrospinal fluid are also associated with more rapid cognitive decline in PD [22, 119].

5.2 Management

No disease-modifying treatments affecting cognition in PD are available and no pharmacological intervention has been demonstrated to affect the transition from PD-MCI to PDD. Whether caffeine and green tea, which appear to reduce the risk of developing PD, have a role in cognitive decline needs further exploration [120, 121].

In PDD, cholinesterase inhibitors are established treatments, with evidence supporting the use of rivastigmine [122] and donepezil [123]. Positive, though modest, effects are reported on cognition, but also on activities of daily living and behavioural disturbances. Rivastigmine is the only cholinesterase inhibitor approved for the treatment of PDD in most countries and thereby widely used. There are yet no convincing differences to donepezil in efficacy, and choice of medication should largely rely on clinical considerations and patient preference. For example, ease of titration, the once daily administration and the possibly more benign side effect profile favours donepezil [124], while the opportunity of a gradual titration or application as a transdermal patch might make Rivastigmine the preferred choice.

The partial N-methyl-D-aspartate receptor (NMDA)-antagonist memantine has a benign side effect profile, but only small positive global effects in one study [125]. As in PD psychosis, review and discontinuation of medications with central anticholinergic activity is likely to have positive effects on cognition, although a recent study indicated that medications with anticholinergic activity were not associated with more rapid cognitive decline in PD [126-128].

Non-pharmacological measures to improve cognition and potentially prevent or delay cognitive decline include physical exercise and cognitive training. An addition to improving

motor symptoms, exercise has been shown to improve cognition, mood and sleep. Aerobic or resistance exercise can improve cognition in PD, with evidence to suggest a positive effect of aerobic exercise on executive function [129]. Cognitive training improves executive functioning, working memory and processing speed in cognitively normal or mildly impaired patients with PD [130]. To which extent this benefit translates to cognition in general and is sustained beyond the duration of training needs further testing.

6. Apathy

Apathy, loss or diminished motivation, is a multidimensional syndrome that includes reduced emotions, goal-directed behaviours, and cognitive activity [131]. The proposed diagnostic criteria for apathy has been validated in people with PD [132]. Up to one third of people with PD without depression or dementia have apathy, which is associated with high levels of disability, accelerated cognitive and functional decline, weight loss, poor quality of life [133], high caregivers' burden, poor quality of care, poor rehabilitation, and increased risk of mortality [134-138]. Further, apathy may impair the ability to engage with treatment and care of other motor, cognitive, and behavioural symptoms. Structural and functional neuroimaging studies investigating apathy in PD have reported changes in right frontal lobe, orbitofrontal cortex, fusiform gyrus, insula, postcentral gyrus, inferior frontal gyrus, left middle frontal gyrus, bilateral cingulate gyrus, bilateral inferior parietal gyrus, and right precuneus [138].

6.1 Assessment

Apathy in PD has to be differentiated from depression, fatigue, psychosis, hypoactive delirium, and adverse effects of medications as this is essential for planning appropriate treatment and avoiding unnecessary medication. A good clinical and collateral history, mental status examination, physical examination, use of assessment instruments, and direct behavioural observation help to clarify differential diagnoses. Apathy presents with diminished spontaneous emotions and emotional responsiveness. Self-reported low mood, depressive cognitions, guilt ideas, negative self-appraisal, and diurnal variation are common in depression but not in apathy. Besides, peripheral and central fatigue are common in PD, and more than 77% of people with PD have clinically significant fatigue[139]. Despite the clinical overlap, apathy can be reliably distinguished from fatigue by the absence of physical aspects of fatigue[140]. Moreover, acute onset and temporal correlation with medication changes indicate the possibility of adverse drug effects. A hypoactive delirium is characterised by attentional deficits, fluctuating cognition, physical examination, and relevant laboratory examinations.

Apathy may present alone or in association with other neuropsychiatric symptoms. The G domain of the NPI [3], and the UDPRS's item on apathy [5] can be used to screen for the presence of apathy. Specific instruments, such as the apathy scale [141], the apathy evaluation scale [142], and the Lille Apathy Rating Scale [143], are available for assessment and monitoring the progress of apathy in PD [144].

6.2 Management

Because of limited pharmacological options, non-pharmacological interventions should be tried first, and be continued in combination with pharmacological interventions for managing apathy in PD. These have largely been evaluated in the context of dementia and preliminary evidence support the potential of tailored therapeutic mentally stimulating activities, behavioural activation therapy, psychomotor therapy [145], physical exercise [146], social interaction [147], cognitive communication therapy [148], individualised functional enhancement programme [149], emotion-oriented care [150], cognitive stimulation therapy, live interactive music [151], and multisensory stimulation for improving apathy.

Evidence supporting the efficacy of available pharmacological options for managing apathy in PD is not robust [152, 153]. Preliminary evidence indicate that L-dopa [154], dopaminergic agonists such as pramipexole [155] and ropinirole [156], and the glutamatergic antagonist amantadine [157] may improve apathy. However, clinical use of these medications has to be balanced with their adverse effects and their effects on other symptoms of PD. Psychostimulants have been tried to treat apathy in PD [158]. A small RCT has reported that methylphenidate could significantly improve apathy in people with dementia, who had moderate to severe apathy at baseline [159]. Another RCT evaluating the efficacy of atomoxetine in PD did not find any significant change in the severity of apathy [160].

Acetylcholinesterase inhibitors have level II evidence to support their efficacy for managing apathy in non-PD dementia [152, 161]. Rivastigmine has been reported to improve the apathy in PD [162], but a recent longitudinal study did not confirm a prolonged effect after one year follow-up [163]. Antidepressants that are effective for the management of depression in PD have not been found helpful in the management of apathy in PD, for example the use of SSRIs has been associated with greater apathy in a retrospective chart review [157, 164, 165]. Prevailing evidence does not support the use of antipsychotic medications for treating apathy in PD, but stopping long-term antipsychotic medication may lead to worsening of apathy [166]. In the absence of robust evidence, optimising the dosage of dopaminergic medication and adding an acetylcholinesterase inhibitor are the first-line pharmacological options available for the off-label clinical management of apathy in PD.

There is little evidence to support the use of repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), ECT, or of transcranial direct current stimulation for managing apathy in PD. There have been reports of worsening of apathy following subthalamic and pallidal DBS [167, 168]. Withdrawal from dopamine agonist drugs and post-operative mesolimbic dopamine denervation may lead to new-onset apathy in people with PD [169]. A case series has reported short-term statistically significant improvement of apathy following rTMS [170].

7. Conclusions

Neuropsychiatric symptoms represent an important aspect of the clinical spectrum of PD, and a particular clinical focus needs to be on consistent recognition [171]. Simple psychosocial strategies should nearly always be considered, either face-to-face or remotely. Importantly, dopaminergic medications can improve or worsen neuropsychiatric symptoms, and thus reviewing the anti-parkinson regime is an important step before commencing psychotropic treatment. In addition, patients with PDD should be considered for cholinesterase treatment.
If depressive symptoms do not respond psychosocial interventions, SSRI or SNRI should be considered. Clozapine is the only antipsychotic supported by convincing evidence, but the risk for agranulocytosis and associated administrative hurdles have led to low prescription rates. Pimavanserin is a potential new agent but currently not available in Europe.

Figures:

Figure 1 Management flow-chart for depression in PD

CBT = Cognitive behaviour therapy; ECT = Electro-convulsive therapy; GDS-15 = 15-item Geriatric Depression Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; HAM-D = Hamilton Depression Rating Scale; SNRI = Serotonin–norepinephrine reuptake inhibitor; SSRI = Selective Serotonin Re-uptake Inhibitors; TCA = Tricyclic antidepressants

Figure 2 Management algorithm for PD psychosis

The right of the figures shows treatment options and considerations at different stages of PD psychosis. The dotted line indicates ongoing review of medication, general health and vision at the point of medication onset. Brackets indicated medications / ECT where clinical trial evidence for efficacy in PD psychosis is limited. See text for further details.

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Screen for presence of depression:
- One positive answer on Two-question screening test
- Score of $\geq$ 5 on GDS-15

Establish clinical diagnosis of depression
- Rule out other organic causes
- Assess if depression related to 'off' periods or non-motor fluctuations. These require adjustment of dopaminergic medication (consider Pramipexole).
- Establish severity of depression (e.g. MADRS, BDI, HAM-D)

Mild depression

- Self-help CBT
- Individual or group CBT
- Physical activity (e.g. exercise groups)
- Sleep hygiene
- Support group
- Carer involvement

Moderate or severe depression

Antidepressant   and/or   Individual or group CBT

1st line: SSRI
- Citalopram
- Sertraline (especially if relevant cardiac disease)
- Paroxetine

If quick resolution of symptoms required and no relevant cardiac disease: TCA
- Nortriptyline
- Desipramine (Imipramine)

No effect after 3-4 weeks at therapeutic dose

Poorly tolerated

Switch to a different antidepressant (consider switching SSRI to venlafaxine/TCA)

Switch to a different antidepressant (preferably use SSRI)

No effect after 3-4 weeks at therapeutic dose

- If no effect: consider adding pramipexole or other antidepressants
- If life-threatening/psychotic depression or patient's preference: consider ECT

Minor symptoms

- Dopamine therapy review
- Review anti-muscarinic load
- Infection / delirium screen
- Optimise vision

Further investigations if hallucinations not typical of PD

Hallucinations with insight

- Reassurance
- Education
- Self- help strategies

If symptoms distressing

Hallucinations without insight Delusions Misidentification

- Psychological intervention
- Cholinesterase inhibitor
- Pimavanserin
- Clozapine
- (Quetiapine)

- (Apomorphine)
- (ECT)