



Published in final edited form as:

*Mov Disord.* 2009 November 15; 24(15): 2175–2186. doi:10.1002/mds.22589.

## Neuropsychiatric symptoms in Parkinson's disease

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### Abstract

Neuropsychiatric symptoms are common in Parkinson's disease, even at the earliest stages, and have important consequences for quality of life and daily functioning, are associated with increased carer burden and increased risk for nursing home admission. In addition to cognitive impairment, a wide range of neuropsychiatric symptoms have been reported. In this paper, the epidemiology, clinical course, diagnosis, and management of some of the most common neuropsychiatric symptoms in PD are discussed: depression, anxiety, apathy, fatigue and psychotic symptoms. Although much is known regarding the prevalence and course of these symptoms, the empirical evidence for how to manage these symptoms is limited at best. There is thus an urgent need for systematic studies for the pharmacological and non-pharmacological management of these symptoms.

### Introduction

Neuropsychiatric symptoms including depression, anxiety, apathy and psychosis[1] are common in Parkinson's disease (PD), affecting the majority of patients at some time during the course of disease. Among the most common, and most important, neuropsychiatric symptoms in PD are depression, anxiety, apathy and psychosis[1]. In this paper which was solicited from the Movement Disorders Society Meeting in Chicago in 2008, we will review the epidemiology, clinical characteristics, and management of these neuropsychiatric symptoms in PD.

### Depression and Anxiety

#### Prevalence and pattern of occurrence

Symptoms of depression and anxiety are common in Parkinson's disease (PD), and depression scores are closely associated with patient-perceived health-status in patients with PD[2].

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**Author roles** Research project: This was an invited review based on the syllabi of a session on "Neuropsychiatric symptoms in Parkinson's disease –Beyond Dementia" at the Movement Disorders conference in Istanbul, 2008.

Statistical Analysis: Not applicable.

Manuscript: Anette Schrag wrote the section on Depression and Anxiety, Laura Marsh the Section on Fatigue and Apathy, and Dag Aarsland the section on Psychosis. All authors reviewed and approved the final manuscript.

No conflicts of interest to report

Approximately 30–40% of patients with PD have significant depressive symptoms, with lower prevalence rates in population-based studies[3–5]. Anxiety affects up to 40% of patients with PD[6–11]. Symptoms of both depression and anxiety can be off-period related phenomena, which are usually, but not always, seen in parallel to motor fluctuations, and can then be particularly severe but respond to antiparkinsonian medication[12–15].

Both depression and anxiety can predate motor symptoms by several years and belong to the non-motor features that may herald the development of PD[16]. Whilst depression may occur reactively, or coincidentally, there is no doubt that at least in part it is an integral part of PD. The pathophysiology of these complications is complex and probably includes dopaminergic, serotonergic and noradrenergic mechanisms. Postmortem studies have implicated serotonergic and noradrenergic structures such as the raphe nuclei and locus coeruleus, which are thought to be involved in the development of depression and are both involved early in the course of PD[17,18]. Cerebrospinal fluid levels of the serotonin metabolite 5-hydroxyindoleacetic acid have also been correlated with severity of depression in PD[19]. There is considerable evidence that dopaminergic dysfunction also plays a role. Dopaminergic projections from the ventral tegmentum of the midbrain to the medial temporal and orbitofrontal regions have been shown to be affected in post mortem studies[20]. In addition, there is evidence from imaging studies that limbic noradrenergic/dopaminergic pathways are dysfunctional in PD patients with depression compared to those without[21]. There also appears to be a genetic predisposition, as first degree relatives of patients with PD are more likely to have had depression or anxiety [22].

### **Clinical characteristics of depression and anxiety in PD**

The key characteristics of depression are low mood and lack of interest or pleasure (anhedonia), one of which is required for a diagnosis of depression in most classifications. Other features of depression can be present in varying combinations but many of these, such as altered appetite or sleep, weight change, loss of libido, psychomotor retardation, reduced memory and loss of energy can overlap with the symptoms of PD, making diagnosis of depression in PD difficult. Some features of depression may also be less common in patients with PD, such as feelings of guilt or worthlessness and suicidal ideation [23,24]. However, in patients who have undergone subthalamic nucleus (STN) deep brain stimulation (DBS), suicide rate is increased, and was the most common cause of post-operative mortality in a study of more than 5,000 patients who underwent this procedure[25], and vigilance towards occurrence of suicidal ideation has been advised[26–29].

Particularly in patients with advanced PD, there can be considerable difficulty in distinguishing somatic symptoms of depression from those of PD, such as slowness of movement and thinking, loss of appetite and weight, or sleep problems. The association with other symptoms of depression or PD and specific symptom characteristics (e.g. fatiguability of movement in bradykinesia vs overall slowness in psychomotor retardation, the pattern of slowness of thinking in depression as opposed to that in cognitive impairment, or the temporal pattern of sleep disturbances and their association with immobility) can be helpful in distinguishing whether symptoms are due to PD or depression. However, this differentiation can be difficult even for an experienced clinician.

The most common anxiety disorders in PD are panic attacks (often during off-periods), generalised anxiety disorder (GAD), simple and social phobias. Outside off-periods, there is no clear relationship to severity of motor symptoms or dementia, but anxiety may be part of an underlying depressive disorder.[30] The relationship of antiparkinsonian medication to anxiety in PD needs further clarification.

## Diagnosis, Assessment and Classification

The most commonly used diagnostic classification for depression and anxiety is the DSM IV-TR[31]. As application of these criteria may miss a substantial number of patients with depression in PD (dPD), an NINDS/NIMH working group on depression and PD[32] issued the following recommendations: I) The diagnosis of dPD should be made according to DSM diagnostic criteria using an inclusive approach, using all symptoms irrespective of potential aetiological basis, as it has the greatest sensitivity and reliability and does not require clinical judgment; II) subsyndromal depression should be included as a diagnostic category in research studies; III) the timing of assessment should be specified (“on” versus “off”-periods) (it should however be noted that most instruments specify  $\geq 2$  weeks as a time frame); IV) informants should be used for cognitively impaired patients; and V) anhedonia should only be diagnosed based on loss of pleasure rather than loss of interest (as it overlaps with apathy) for diagnosis of minor depression/subsyndromal depression. These modified DSM criteria require further validation. As there is significant association between low mood and anxiety symptoms, it has also been suggested by others that these should be added to the DSM diagnostic framework [33]. The diagnosis of minor depression is based on the same symptoms, but only requires presence of 2–5 symptoms in the DSM IV-TR classification, and dysthymia requires that depressed mood has been present on most days for at least two years with at least two out of 6 other symptoms.

Clinimetric rating scales are often used in large-scale epidemiological and other studies as they do not require clinical judgment and are quantifiable. As they have diverse properties and differing clinical applicability their use should be tailored to the purpose of the individual study or purpose (see table 1). Generally, observer-rated scales are preferred if the study or clinical situation permits. For screening purposes, the Hamilton Depression Scale (HAM-D), the Beck Depression Inventory (BDI), the Hospital Anxiety and Depression Scale (HADS), the Montgomery-Asberg Depression Rating Scale (MADRS) and Geriatric Depression Scale (GDS) have been shown to be valid in depression in PD. For measurement of *severity* of depressive symptoms, the Ham-D, MADRS, BDI and Zung Self-Rating Depression Scale (SDS) scales are useful instruments. The Cornell Scale for the Assessment of Depression in Dementia (CSDD) is valid for the assessment of depression in patients with dementia. However, a diagnosis of depression should only be made using clinical criteria rather than scales. As the differentiation of overlapping symptoms of depression and PD remains difficult, clinical ratings scales should be used only with adjustment for severity and change in PD symptoms using appropriate scales (e.g. UPDRS).[34]

The application and clinical validity of DSM anxiety criteria in PD has not undergone the same systematic analysis and critique as depression but suffers the same conceptual difficulties and problems with symptomatic overlap. In addition, it should be noted that social phobia should not be diagnosed if the fear is only about being embarrassed by PD symptoms in public. Several rating scales for anxiety have been used in patients with PD, but their validity needs to be assessed further[8].

## Management

The first important issue is to determine whether the depression and/or anxiety symptoms occur solely in off-periods (see above). If so, adjustment of antiparkinsonian medication is required and usually successful (personal observation). This may be obvious, but not uncommonly prolonged neuropsychiatric symptoms are due to under-medication and may be difficult to identify as off-period related.

If depression or anxiety symptoms are not due to non-motor fluctuations, the severity of symptoms should be determined to assess the need for treatment. In most cases with mild

depression (which are the majority), non-pharmacological intervention is the treatment of choice, with treatments ranging from counselling and patient education to cognitive-behavioural therapy[35].

One should bear in mind when assessing open-label studies and individual patient response, that there is a very large placebo-response in response to antidepressant trials in PD. There is a lack of large, well-designed randomised placebo-controlled trials of antidepressant and anxiolytic treatments[36–38]. There are several approaches to treatment of dPD: psychotropic medication, dopaminergic medication, electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS).

**Dopaminergic**—As many patients will already be on dopaminergic medication and/or also require improvement of motor symptoms, optimisation of existing treatment may be the most pragmatic first step. Although no class I evidence from controlled trials in PD is available at the time of writing, dopaminergic medications have been suggested to improve depressive symptoms in PD. Pramipexole has been reported in double-blind trials to be effective for both unipolar and bipolar depression in non-PD patients. In PD, several studies without placebo control reported improvement of depression scores in depressed patients with PD, and a double-blind trial of ropinirole extended-release preparation reported improvements in depression scores[39]. However, in the double-blind ropinirole study the patients were not selected according to criteria for depression and the primary study outcome was motor function. In addition, given the overlap of features of depression and PD, the antidepressant effect of these medications is difficult to ascertain since the studies did not control for improvement of motor symptoms. The results of an ongoing placebo-controlled trial of pramipexole in depression in PD are currently awaited.

**Psychotropic**—Pharmacological agents used for dPD include tricyclic antidepressants, tricyclic-related drugs (trazodone), selective serotonin reuptake inhibitors (SSRI), the serotonin and noradrenaline re-uptake inhibitor (SNRI) venlafaxine, the selective noradrenaline re-uptake inhibitor reboxetine, and the pre-synaptic alpha-2 adrenoceptor antagonist mirtazapine. There is a suggestion that antidepressant medications in PD are less effective than in depressed non-PD patients, although older patients and those with major depression may have a better response[38]. In one meta-analysis (11 studies, 2 placebo-controlled)[38], there was a large composite reduction in depression rating scales in both active treatment and placebo groups but no statistically significant difference between the two groups. In another (only 6 studies met criteria for inclusion, 3 placebo-controlled)[40], it was concluded that there is some evidence for the antidepressant effectiveness of amitriptyline in PD patients (with the caveat of potential side effects) and that SSRI have not been demonstrated to have clear efficacy compared to placebo. In clinical practice nortriptyline is generally preferred in practice to amitriptyline due to its better side effect profile. A small recently published placebo-controlled study reported that nortriptyline was more effective than placebo in improving depressive symptoms, but there was no significant benefit in the group of patients taking paroxetine CR compared to the placebo group[41]. On the other hand, another small placebo-controlled trial found that both desipramine, a predominantly noradrenergic reuptake inhibitor tricyclic, and citalopram led to improvement of depressive symptoms after 30 days [42].

Consideration should be given to the potential side effects related to these medications, particularly in the elderly, their possible interaction with other drugs (particularly those metabolised via the cytochrome P450 system) resulting in variations in plasma concentrations, reports of exacerbation of motor function and their potential to exacerbate non-motor and dopaminergic drug-related complications of the disease. Tricyclics are generally less well tolerated than SSRIs[42]. SSRIs potentially have important pharmacological interactions with

the MAO-B inhibitors selegiline and rasagiline and thus theoretical predilection to a serotonin-syndrome. This effect is likely to be rare given that at therapeutic doses MAO-B inhibitors produce no significant MAO-A inhibition, but should be considered.

Atypical neuroleptics may have a role in treating depression with co-morbid psychotic features, although these may respond to antidepressants alone[43].

There has been no systematic assessment of anxiolytic treatment in PD. The SSRI are currently favoured as treatment of anxiety disorders in PD but their therapeutic efficacy is yet to be demonstrated. Benzodiazepines should be used with caution as they can increase the risk of falls and cognitive, autonomic and sleep-related side effects are likely to be common in PD (although clonazepam can be useful as a treatment of REM-sleep behaviour disorder), and clomipramine shares the anticholinergic side-effect of other tricyclics. Small studies have reported effects of neuromuscular (massage) therapy, STN-DBS and psychotherapeutic treatment[8,44,45]. Anxiolytic treatments that have not yet been assessed in PD include pregablin and venlafaxine.

### Other options

A small placebo-controlled pilot trial recently reported significantly greater improvement of depression in patients treated with omega-3 fatty-acid supplementation[46]. Bright light therapy has also been reported to be slightly superior to placebo (with less bright light) in a trial[47]. The results of these small trials require further study.

STN-DBS has been reported to improve depression and anxiety scores in the majority of patients who underwent this procedure for improvement of motor symptoms, but significant psychiatric disease has been an exclusion criterion in most studies, and suicidal ideation is a risk following this procedure (see above). At present, this should therefore not be considered a treatment option for depression or anxiety in PD.

rTMS has been reported as a promising option for dPD, but no large controlled trials are currently available[48–50].

ECT is reserved for severe, treatment resistant cases of depression, and can be a life-saving procedure in selected cases[51–53]. However, no sufficient trials in PD are available.

## Apathy and fatigue

### Introduction

Apathy and fatigue are two common non-motor disturbances in patients with Parkinson's disease (PD) that contribute substantially to disability and are attributed to basal ganglia pathology and disturbances in frontal-subcortical connections[54]. For both, mood symptoms and cognitive deficits are also frequently present. Appreciation of the overlap among motor, cognitive, and psychiatric phenomena along with the specific features of apathy and fatigue in patients with PD facilitates recognition of each and the likelihood that symptoms will be addressed. However, only a few studies have addressed apathy or fatigue in PD and improved detection and effective treatments are needed.

### Prevalence and pattern of occurrence

Apathy and fatigue can present as a feature of another condition or as independent and clinically significant symptoms. Most studies have used symptom rating scales to define the presence of apathy. Reported prevalence, ranging from 17% to 70%[1,55–59], is influenced by the extent of cognitive impairment and depressive symptoms in the sample, the assessment tools used, and the rater (i.e., a clinician, family member, or patient)[1,57,59,60]. Apathy symptoms in the



absence of depression occur in 4% to 30% (14% average prevalence), whereas reported prevalence for depression in the absence of apathy is 6% to 28% and for the combination of apathy and depression is 12% to 47% [1,54–58]. Apathy, also a feature of dementia, delirium, and demoralization, and can occur in the absence of cognitive decline [4,54]. The longitudinal course of apathy has not been studied.

Fatigue, the single most disabling symptom reported by up to 1/3 of patients with PD [61,62], has a prevalence of 32% to 58% that is also influenced by inconsistent definitions of fatigue and which assessment instrument was used [61,63,64]. Fatigue is present early in the course of PD and may even predate onset of motor features [65]. Once present, fatigue can be chronic or intermittent, but lifetime prevalence increases over time [64]. Fatigue in PD is also associated frequently with depression, cognitive deficits, and daytime sleepiness [64,66,67]. Despite its prevalence and impact, fatigue is under-recognized clinically [68].

### Clinical characteristics

Apathy refers to a set of behavioral, emotional and cognitive features that involve reduced interest and motivation in goal-directed behaviors, indifference, and flattened affect [69]. Some studies emphasize lack of motivation whereas others focus on lack of emotional responsiveness as a core feature. Patients typically show poor motivation with reduced initiative, effort, and perseverance as well as indifference to their circumstances. This is manifest as a lack of spontaneous engagement or early withdrawal in activities, a lack of concern for one's own health, or the absence of curiosity about others or new experiences. The impact of apathy is considerable; the patient is generally inactive, and this passivity leads to further functional decline and greater debility [1,55,58,59]. Families misattribute signs of apathy as evidence of laziness, entitlement, or contrariness. Thus, providing care can be unrewarding and lead to resentment, especially when apathy remains undiagnosed [60].

The role of depressive disturbances in the presentation of apathy is an important consideration. Reports are inconsistent as to whether the combination of apathy and depression is more common than apathy without depression or depression without apathy [54,57,58]. At issue is whether loss of goal-oriented cognition, a feature of Marin's criteria for an apathy diagnosis [70], qualitatively represents the same phenomenon as the reduced interest and anhedonia that is characteristic of depressive disorders. In addition to overlapping diagnostic criteria, symptom rating scales also include items that overlap features of depression and apathy. The Neuropsychiatric Inventory is an exception in this regard, but apathy and depressive subscores were still significantly correlated in a study involving PD subjects [55]. By contrast, apathy and depression were more clearly dissociated in other disorders in that study, such as progressive supranuclear palsy.

Cognitive impairment, another important clinical factor in apathy, is also a general feature of PD. Apathy in PD is associated with bradyphrenia, global cognitive impairment, and executive dysfunction [54,56,59]. However, motor severity, l-dopa dose, physical disability, and PD duration are less likely to be associated with apathy [56,58].

There are two main classifications of fatigue: peripheral and central [43]. Peripheral fatigue is a physiological phenomenon that involves lack of energy associated with muscular fatigue. It is objectively measured by decreased force generation or the inability to sustain repetitive movements [65]. More clinically relevant in most cases is central fatigue, which is generally described as an abnormal degree of persistent tiredness, weakness, or exhaustion that is mental, physical or both in the absence of motor or physical impairment. [65] Central fatigue is a subjective experience (in contrast to apathy, which is generally an observed phenomenon) with two subtypes, physical and mental. Physical fatigue represents the sense of physical exhaustion and lack of energy to perform physical tasks despite ability to do so. Mental fatigue refers to

the effects experienced during and after prolonged periods of demanding cognitive activities that require sustained mental efficiency. Given its subjective nature, the overlap between physical and mental fatigue is not always clear.

In interviews of patients with PD, fatigue was described as unpredictable with respect to its onset, duration, and relationship to prior activity, but often exacerbated by physical, psychological, or social stressors[71]. Inability to initiate and sustain activity associated with fatigue is distinct from sadness, sleepiness, or impaired motor function[71]. Fatigue has adverse effects on quality of life, depression, and disability in PD[72] and is the primary determinant of work-related disability[73]. Relationships between fatigue and motor symptoms, daytime sleepiness, sleep quality, and physical activity are inconsistent[60,64]. Surprisingly, fatigue is unrelated to exercise efficiency, activity level, or physical fatigue[65].

Fatigue in patients with PD is associated with higher rates of depressive symptoms, sleep disturbances, and cognitive disturbances, but it is also highly prevalent in non-depressed patients[64]. In one series, 43.5% of patients without depression, dementia, or sleep problems still reported fatigue, in contrast to 4.5% of controls[74]. By definition, mental fatigue involves difficulties initiating and maintaining sustained cognitive performance and is often associated with motivational and attentional difficulties[65]. For example, mental fatigue during driving may lead to reduced error monitoring. In contrast to apathy, which appears to be associated with pre-existent cognitive impairment, especially executive dysfunction, fatigue occurs as a consequence of mental challenges. In particular, tasks involving increased attentional demands and multi-tasking may be more likely to be associated with fatigue[67].

### Diagnosis, Assessment and Classification

For both apathy and fatigue, co-existence of mood symptoms and cognitive deficits, and their overlap with motor signs of PD, contribute to diagnostic challenges. For example, loss of motivation, a lack of effort, and emotional indifference mimic bradykinesia, bradyphrenia, and masked facial expression of PD in the absence of apathy[60]. Similarly, flattened affect and passivity can manifest as monotonous and reduced spontaneous speech, which can be functions of hypophonia or cognitive dysfunction.

Establishing the diagnosis of apathy can be challenging for additional reasons. Apathy, which can represent a transient clinical state or an isolated symptom or syndrome, is defined inconsistently in the literature and lacks standardized or validated criteria for apathy. Marin's criteria of reduced goal-directed behavior and cognition and emotional concomitants of goal-directed behavior are the most widely used[69]. Controversy over the roles of an emotional dimension and cognitive deficits make it difficult to apply these criteria in PD. Discrete criteria for apathy are also lacking in the DSM-IV-TR.

Several rating scales, recently reviewed by a Movement Disorder Society task force, assist with evaluation[75]. Rating instruments are generally useful as screening tools to be used with a secondary diagnostic interview. The rater (patient, caregiver, or clinician) influences the quality of the information obtained. For example, patients with apathy may be indifferent as to whether they have undergone behavioral changes. Distinguishing apathy from depression requires evidence for emotional features such as low mood, a reduced sense of pleasure, guilt, diminished self-attitude, and anxiety in patients with a concurrent depressive disorder.

The diagnosis of fatigue is challenging because of its recognition as an independent entity that can also be a feature of other disturbances. For example, fatigue is one of the criteria for diagnosing major depression. It can be impossible to distinguish fatigue due to depression from that related to other factors. However, assessments of fatigue must account for the possibility of a depressive disturbance.

A number of fatigue rating scales have been developed for the general population and for specific conditions[76]. Unidimensional fatigue scales provide a single score that represents the range of symptoms and behaviors whereas multidimensional scales provide a profile of various qualitative and quantitative aspects of fatigue. The Parkinson's Fatigue Scale (PFS) was developed as a disease specific scale to overcome limitations of generic scales, which do not account for motor symptoms and to measure the single construct of physical fatigue[71]. Most fatigue scales use set cut-off scores to define presence or absence of clinically significant fatigue.

## Management

Optimal management of apathy and fatigue involves vigilance for the symptoms of each, use of informants to obtain information to establish clinical diagnoses, and judicious use of assessment tools to screen for the presence of non-motor symptoms. Treatments for both include illness education to families and patients about depression, fatigue, apathy, and cognitive disturbances in PD, behavioral strategies to maximize executive functions, and use of medications to treat mood disorders and cognitive disturbances; improvements in co-morbid conditions may be sufficient to relieve apathy and fatigue when they do occur.

Studies on the specific treatment of apathy in PD are limited. Management is often difficult since patients are indifferent to the need to attend to their own health and well-being and their inactivity can be misconstrued as “characterological laziness”[77]. Non-pharmacologic strategies involve providing an individualized daily schedule and structure with varied activities and group experiences that help to maintain a satisfactory activity level and enrichment. Campbell and Duffy underscore the role of the family as a therapeutic resource as patients benefit from a “goal-directed, reality-based, and paternalistic approach that essentially allows the caregiver to function as an `auxiliary executive”[77]. Possible medications include dopamine agonists, psychostimulants, modafinil, dopamine agonists, and testosterone[60,62, 77]. Deep brain stimulation effects on apathy are inconsistent[62].

Few studies have investigated treatment of fatigue. In placebo-controlled trials, methylphenidate had a favorable effect on fatigue[78] and l-dopa improved physical fatigue [79]. Dopamine agonists have been helpful for some, but fatigue worsened in the placebo group compared to those who initiated levodopa therapy in early course untreated PD[80]. Whereas modafinil, a wake-promoting drug, improved excessive daytime sleepiness but not fatigue in PD in a double-blind placebo-controlled trial[81], nocturnally administered sodium oxybate improved fatigue and excessive daytime sleepiness in PD[82].

## Hallucinations and Psychosis

### Definitions

Psychotic symptoms include visuo-perceptual symptoms such as visual hallucination (VH), illusions, passage and presence phenomena (See table 2 for definition of these phenomena). Hallucinations may also occur from other modalities, mainly auditory, but usually in combination with VH. In addition, thought disorders, typically delusions, may occur. Psychotic symptoms may be mild or severe, occur together or single, be accompanied by insight of the pathological nature of the symptom or nor, and may be accompanied by affective and behavioural disturbances and require psychiatric hospitalization.

### Epidemiology

Psychotic symptoms are a frequent occurrence in PD. The frequencies vary according to the definition used. If mild forms are included, psychotic symptoms may affect up to 50% of patients.[27] Studies on psychosis have mostly focused on visual hallucinations, the most



common type of psychotic symptom in PD. However, hallucinations can occur in all sensory domains and delusions of various types are also relatively common[83]. Relatively few longitudinal studies of the course of PD exist. However, psychotic symptoms, once present, tend to be persistent and progressive[84].

### **Clinical presentation**

The typical VHS consist of persons, who may or may not be familiar, and less often animals or objects. They may be numerous, but often single or few in numbers. They are usually complex, and stereotype in a given patient. They appear suddenly, often move, and usually seem very real. They usually vanish suddenly, sometimes when the patient tries to ascertain their reality by approaching or touching them, or asking other people to confirm their presence. They often occur in dim light, often at night. Insight in the pathological nature of the phenomenon may or may not be present. Lack of insight is more common in subjects with cognitive impairment.

Capgras and similar misidentification phenomena may also occur. Typically, the patient thinks that his spouse is someone else and not his or her spouse, which may create challenging situations with affective and behavioural changes. Other forms of delusions are relatively rare, but are often persecutory, or focus on infidelity.

The neuropsychiatric symptoms in PD tend to cluster into distinct syndromes. In a recent study, five clusters were identified. The largest group showed symptoms of mild depression, followed by a group with hallucinations and mild other symptoms. One group had sleep disturbances exclusively, and another showed apathy, anxiety and depression. A small group showed a variety of severe symptoms, including psychosis and agitation[85].

### **Assessment and diagnosis**

Recently, consensus criteria for PD associated psychosis was proposed after a NIH-sponsored workshop [86]. However, psychotic symptoms are not always reported voluntarily, and the clinician should ask for these phenomena. Some patients may deny or refuse to report these symptoms, or, in dementia, may have forgotten, and thus a caregiver should be questioned as well. The frequency, intensity and impact of the symptoms should be noted, as well as the situation and circumstances in which they occur, the detailed phenomenology, and any other accompanying symptoms such as cognitive impairment, depression, anxiety, sleep disorders. There are several rating scales in use, although no generally accepted ones. Item 2 of the UPDRS subscale 1 can be used, and also the Neuropsychiatric Inventory. More detailed assessments can be made using specific scales such as Parkinson Psychosis Rating Scale. An MDS Task Force recently reviewed the different scales, listed their strengths and weaknesses and provided some guidelines regarding recommendations[87].

### **Aetiology**

Psychotic symptoms develop from a complex interplay of extrinsic and intrinsic factors. It was previously considered that VH in PD were caused by the dopaminergic medications. However, it is now generally accepted that although dopaminergic drugs, in particular dopamine agonists, can contribute to the emergence of psychosis, other factors may be more important, such as dementia and visuospatial impairment, as well as general factors such as old age and more advanced disease stage. Brain changes found to be associated with an increased risk for psychotic symptoms in PD include cholinergic deficits and Lewy bodies in the temporal lobe. Pathological excitation of the visual pathways due to physical or chemical factors may contribute. Psychotic symptoms are frequent during night and associated with sleep-disturbances, and vivid dreams and sleep-related phenomena may lead to hallucinations[88].

## Clinical consequences

The impact of psychosis is substantial in that it is associated with dementia, depression, earlier mortality, greater caregiver strain, and nursing home placement[1,89]. Thus, it is crucial to identify these symptoms in order to optimize the management of PD patients.

## Management

**Non-pharmacological**—Psycho-educative approaches, such as information and guidance about the nature of the phenomena may help, as well as cognitive approaches such as distraction or re-directing attention. Environmental interventions such as improving light-conditions and visual aids may also be useful [90]. Searching for potential contributing medical factors is always important, such as pain, infection, dehydration, metabolic disturbance, sensory deficits, and recent changes in the medication.

**Pharmacological**—First line is always to attempt adjustment of the antiparkinson treatment. Reduction of dose or number of drugs may reduce the symptoms, even without worsening of motor symptoms. According to expert opinion, anticholinergics should be withdrawn first. It is usually recommended to withdraw selegiline, amantadine and dopamine agonists before changing the levo-dopa dosage.

The only adequately tested drug to recommend is clozapine, which has been shown to improve VH without worsening motor symptoms[91]. However, randomised placebo-controlled trials have been conducted in patients without dementia only. The risk of agranulocytosis necessitates regular blood test. Other antipsychotic agents such as risperidone and olanzapine, are less useful, due to being less effective and with a higher risk for adverse events including motor worsening, cognitive decline and, drowsiness and confusion[40]. Initial open-label reports on quetiapine were promising, although two placebo-controlled trials were negative. More novel antipsychotics, such as ziprasidone and aripiprazole, have not yet been tested systematically and preliminary reports are inconclusive. For a review, see [92]. Careful monitoring is required, and dosing should be low with small increments. Recent reports have high-lighted that antipsychotic agents have a risk of cerebrovascular incidents and increased mortality, as well as worsening of cognition, in elderly people with dementia[93].

Cholinergic agents may improve neuropsychiatric symptoms in PD, but there is yet no evidence-base to supporting their use for VH in PD. However, rivastigmine seems to be particularly useful for PD with VH, in that the rapid cognitive decline in this group can be reduced[94].

## Acknowledgments

The authors want to thank Ms Karen Simonsen for expert technical assistance.

**Financial Disclosure:** Dr. Marsh is supported by NIH grants [RO1-MH069666 and the Morris K. Udall Parkinson's Disease Research Center of Excellence at Johns Hopkins (NIH-P50-NS-58377)].

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Table 1

Neuropsychiatric features in PD: Frequency, diagnostic features, assessment and treatment

Syndrome	Subtype	Prevalence %/key feature	Diagnostic criteria in PD/Rating scale	Treatment (unless off-period related)
Depression	Major depression	10–30%	NINDS-NIMH[32] Low mood or loss of interest/pleasure	No large controlled trials published to date[36–38] Non-pharmacological (counseling, CBT), dopamine agonists (pramipexole, ropinirole), antidepressants (tricyclics, trazodone, SSRIs, SSNRI, SNRI, mirtazapine)
	Minor depression	10–20%	NINDS-NIMH[32] Low mood and/or loss of pleasure	No available evidence
Anxiety	Dysthymia	10–20%	NINDS-NIMH[32] Low mood > 2 years	No available evidence
	Total	30–40%	none	Poor evidence Benzodiazepines, clomipramine, non-pharmacological
	Panic attacks/panic disorder	4–30%	None Episodic attacks of panic	Same as above
	GAD	10–15%	None Excessive and often irrational anxiety or worry	Same as above
Psychosis	Hallucinations	40–50%	NINDS-NIMH (1861) Seeing imaginary people or animals	I Clozapine Little evidence for other antipsychotic agents
	Delusions	5–10%	Same False, fixed, idiosyncratic beliefs that are maintained despite evidence to the contrary.	Same
Apathy [75]		17–70%	None Lack of initiative, motivation	Limited evidence: Dopamine agonists, stimulants, modafinil
Fatigue [62]	1) Peripheral 2)Central (Mental and Physical components)	32–58	None Peripheral refers to muscle fatigue. Central fatigue involves abnormal persistent tiredness and weakness	Limited evidence: Methylphenidate, L-DOPA, Dopamine agonists

BDI=Beck Depression Inventory, HAMD=Hamilton Depression Scale, HADS=Hospital Anxiety and Depression Scale, SDS=Zung Self-Rating Depression Scale, GDS=Geriatric Depression Scale, MADRS=Montgomery-Asberg Depression Rating Scale, UPDRS=Unified Parkinson's Disease Rating Scale, CSDD=Comell Scale for the Assessment of Depression in Dementia, CES-D=Center for Epidemiologic Studies Depression Scale, BAI=Beck Anxiety Inventory, SAS=Zung Self-Rating Anxiety Scale, ASI=Anxiety Status Inventory, STAI=Spielberger State Trait Anxiety Inventory, HARS=Hamilton Anxiety Rating Scale, NPI=Neuropsychiatric Inventory, SSRI=selective serotonin reuptake inhibitors, SSNRI=selective serotonin reuptake inhibitor, SNRI=selective noradrenaline re-uptake inhibitor

**Table 2**

Terms and definitions used in this critique (from ref [87]):

<b>Term</b>	<b>Definition</b>
<i>Psychosis</i>	the full spectrum of features seen in PD psychosis, including hallucinations and delusions and the “minor” phenomena of illusions, ‘passage hallucinations’ and ‘sense of presence’
<i>Hallucinations:</i>	are abnormal perceptions without a physical stimulus that can involve any sensory modality and may be simple or complex in form.
<i>Illusions</i>	are misperceptions of real stimuli that are often visual in nature
<i>Delusions:</i>	false, fixed, idiosyncratic beliefs that are maintained despite evidence to the contrary.
<i>Presence hallucinations</i>	consist of the experience that someone is present when nobody is actually there
<i>Passage hallucinations</i>	fleeting, vague imaging in the peripheral vision