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REVIEW

Treatment of Cognitive, Psychiatric, and Affective Disorders Associated with Parkinson's Disease

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Abstract Neuropsychiatric symptoms are common in Parkinson's disease (PD) and add significantly to the burden of disease. These symptoms are most commonly part of the disease spectrum owing to pathological changes within relevant brain regions. Neuropsychiatric problems include disorders of cognition, ranging from mild cognitive impairment to dementia, psychotic symptoms, including, most commonly, well-formed visual hallucinations and paranoid delusions, and mood disorders, such as depression and anxiety. The other common cause of neuropsychiatric problem is secondary to use of dopaminergic drugs. Some PD patients may develop behavioral disorders, including impulse control disorders (ICDs) and addictive symptoms. Psychosis can be due to a mixture of underlying pathology, with triggering or worsening of symptoms with changes to PD medications. Currently, management of these disorders primarily uses therapies developed for general psychiatry and cognitive neurology, rather than specifically for PD. However, significant adverse effects, such as worsening of the motor symptoms of PD, can limit use of some drug therapies. Identification of drug-induced symptoms, such as ICDs, enables withdrawal of the offending drug as the principal management strategy. Research is ongoing in an effort to develop more specific therapies for PD-related neuropsychiatric symptoms.

Keywords Parkinson's disease · mood · psychosis · dementia · impulse control disorder

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Introduction

Neuropsychiatric symptoms are common in Parkinson's disease (PD) and add significantly to the burden of disease. These symptoms can be part of the disease spectrum owing to pathological changes within relevant brain areas, or due to side effects associated with dopaminergic replacement therapies. Such neuropsychiatric symptoms include disorders of cognition, ranging from mild cognitive impairment to dementia and psychotic symptoms, including, most commonly, well-formed visual hallucinations and paranoid delusions. Mood disorders are common, particularly depression and anxiety, and can predate motor symptoms of PD and may be early symptoms of the disease. Other symptoms include behavioral disorders, including impulse control disorders (ICDs) and addictive symptoms that can occur with use of dopaminergic drugs. Treatment of these disorders primarily uses therapies developed for general psychiatry and cognitive neurology, rather than specifically for PD. Intolerable side effects, such as worsening of the motor symptoms of PD however, can limit the benefit of some drug therapies. To date, there are limited evidence-based medicine conclusions to help the practising clinician with decisions regarding choice of drug or dose, and current best practice is summarized in Table 1. An overview of the largest key double blind, randomized controlled trials (DBRCTs) of each therapeutic target is presented in Table 2. Identification of drug-induced symptoms, such as ICDs, enables either a reduction or discontinuation of the offending drug as the management strategy. In general, understanding the pathophysiology of these neuropsychiatric symptoms has lagged behind the motor symptoms of PD, but recent developments are enabling more focused and better management of these disabling symptoms.

Mild Cognitive Impairment and Dementia in PD

A decline in the cognitive function of PD patients may develop throughout the disease course. Mild cognitive impairment

Table 1 Pharmacologic management of neuropsychiatric symptoms in Parkinson's disease*

Symptom	Medication	Dosage	Common side effects	Serious side effects
PDD	Rivastigmine	1.5–6.0 mg twice daily, skin patch 4.5–9.8 mg/24 h	GI symptoms, bradycardia, vivid dreams, exacerbation of tremor	Heart block
	Donepezil	5–10 mg once daily	GI symptoms, bradycardia, vivid dreams, exacerbation of tremor	Heart block
	Galantamine	4–12 mg twice daily	GI symptoms, bradycardia, vivid dreams, exacerbation of tremor	Heart block
	Memantine	Titrated to 10 mg twice daily	Confusion, dizziness, drowsiness, headache, insomnia, agitation, hallucinations	Extrapyramidal symptoms
Psychosis	Clozapine	6.25–50.00 mg nightly or divided	Drowsiness, dizziness, GI† symptoms	Agranulocytosis, seizures, myocarditis, fast/irregular heart rate, orthostatic hypotension, GI hypomotility
	Quetiapine	12.5–400.0 mg nightly or divided	Drowsiness, dizziness, GI symptoms	Extrapyramidal symptoms
Mood	Citalopram	10–20 mg once daily	Weight gain, drowsiness, sexual dysfunction, nausea	Cardiac arrhythmia, hallucinations, suicide, seizures
	Fluoxetine	10–50 mg once daily	Weight gain, anorexia, nausea, drowsiness, sexual dysfunction, akathisia	Suicidal thoughts, seizures
	Paroxetine	20–40 mg once daily	Weight gain, anorexia, nausea, drowsiness, sexual dysfunction, akathisia	Suicidal thoughts, seizures
	Sertraline	25–200 mg once daily	Weight gain, drowsiness, sexual dysfunction	Suicidal thoughts, seizures
	Venlafaxine XR	37.5–225.0 mg once daily	Drowsiness, sexual dysfunction, dry mouth, insomnia, GI symptoms	Suicidal thoughts, seizures
	Amitriptyline	25–75 mg/day nightly or divided	Anticholinergic effects,‡ drowsiness	Cardiac arrhythmia, heart block, seizures
	Nortriptyline	25–75 mg/day single or divided	Anticholinergic effects	Cardiac arrhythmia, heart block, seizures
	Desipramine	25–75 mg/day single or divided	Anticholinergic effects	Cardiac arrhythmia, heart block, seizures

PDD = Parkinson's disease dementia; GI = gastrointestinal

*All medication usage off-label except rivastigmine; † GI, gastrointestinal; ‡ Anticholinergic symptoms such as cognitive dysfunction, hallucinations, blurred vision, dry mouth, weight gain, urinary retention

(PD-MCI) is present at the time of diagnosis in about 35 % of individuals and in approximately 50 % of all non-demented PD patients after 5 years [1]. There are discrepancies in these figures, with the proportion of patients with PD-MCI differing based on which test (Mini Mental Status Examination, Montreal Cognitive Assessment, full neuropsychological testing) is used; what change in the scale is considered abnormal, for example 1 or 2 SD; how change from "premorbid" function is measured; the type of population sampled; and the duration of follow-up [2, 3]. The most common subtype of PD-MCI is non-amnestic, single-domain impairment [3] (i.e., affecting the domains of executive function, psychomotor speed, visuospatial processing, attention) [4]. Multiple cognitive domains including memory may also be affected, although language is not typically involved [5]. The presence of PD-MCI is a strong predictor of the development of PD dementia (PDD), which may occur in up to 80 % of PD patients over time [4]. However, whether a subtype of MCI (amnestic [6] or non-amnestic [7]) predicts development of dementia is not yet clear.

The diagnosis of PDD, relative to PD-MCI, is similar to that of MCI in patients with Alzheimer's disease (AD), such that dementia is diagnosed when a person develops significant impairment of functional independence. When considering a diagnosis of PDD, however, it is important to keep in mind that other features of PD, including mood disorders and motor symptoms, may also affect functioning [8]. Such symptoms may cause diagnostic challenges. Some patients with parkinsonism develop dementia early on in the disease course—if within 1 year of the motor symptoms the disorder is termed dementia with Lewy bodies (DLB) [9]. The pathology of DLB is the same as PDD, with widespread cortical alpha synuclein deposition [10].

PDD has a negative impact on the quality of life of patients, increases caregiver burden and need for nursing home admission, and increases mortality [3, 11]. In addition to a diagnosis of PD-MCI, other risk factors and correlates for PDD include increasing age and duration of PD, male sex, "atypical" parkinsonian features, such as increased symmetry of parkinsonism, speech, and swallowing difficulties, and presence of gastrointestinal and/or urologic problems at baseline, and other non-motor symptoms, such as visual hallucinations, apathy, depression, and rapid eye movement sleep behavior

Table 2 Key double-blind randomized controlled trials evaluating therapies for neuropsychiatric symptoms in Parkinson's disease

Indication	Medication (dose/day)	Number of patients	Duration (weeks)	Primary endpoints	Results	Reference
PD-MCI	Rasagiline 1 mg	48	12	Neuropsychological testing for each cognitive domain and combined z-score	Compositional z-attention score improved with rasagiline *vs* placebo. Other domains were not significant	[16]
PDD	Donepezil (5 mg and 10 mg)	550	24	ADAS-Cog, CIBIC+	ADAS-cog: NS (but with treatment-by-country interaction analysis, 5 mg and 10 mg/d significant CIBIC+: significant for 10 mg, not 5 mg *vs* placebo	[36]
PDD	Rivastigmine 9–12 mg	541	24	ADAS-Cog, ADCS-CGIC	Both endpoints significant *vs* placebo	[24]
PDD/DLB	Memantine 5–20 mg	195	24	ADCS-CGIC	Significant improvement *vs* placebo in DLB group only	[40]
Psychosis	Clozapine 6.25–50.0 mg	60/60	4/4	CGI-S/CGI-S, motor UPDRS	Both studies significant improvement *vs* placebo. No worsening of motor UPDRS score	[173, 174]
	Olanzapine 2.5–15.0 mg	160 (US study) + 77 (Europe)	3	BPRS positive symptom cluster; motor UPDRS	No significant improvement in BPRS *vs* placebo. Significant worsening in motor UPDRS *vs* placebo	[64]
	Quetiapine flexible; mean 119 mg	58	12	BRPS, CGI-S, motor UPDRS	No significant change *vs* placebo	[73]
Depression	Pramipexole 0.375–3.000 mg	296	12	BDI-II	Significant improvement *vs* placebo	[97]
	Venlafaxine 37.5–225.0 mg	34 (39 placebo)	12	HAM-D17	Significant improvement *vs* placebo	[103] (and see [104])
	Paroxetine 10–40 mg	42 (39 placebo)	12		Significant improvement *vs* placebo	
	Fluoxetine 20–40 mg	7 (9 nefazadone)	12	BDI, CGI-S	Significant improvement *vs* baseline (no placebo)	[175]
	Citalopram 10–20 mg	37	6	HAM-D17	No significant improvement *vs* placebo	[105]
	Sertraline 25–100 mg	6	10	Response rate defined as >50 % improvement in MADRS	No significant improvement *vs* placebo	[106] (and see [176])
	Atomoxetine 80 mg	55	8	Response rate defined as >50 % improvement in IDS-C and CGI-I	No significant changes *vs* placebo	[18]
	Desipramine 75 mg	17 (16 placebo)	4	MADRS	Significant improvement *vs* placebo	[107]
	Nortriptyline 25–75 mg	17 (17 placebo; 18 paroxetine)	8	HAM-D17 and response rate defined as >50 % change in HAM-D17	Significant improvements in both endpoints *vs* placebo (no significant change paroxetine *vs* placebo)	[104]
	Amitriptyline 25 mg	15 vs sertraline (16)	12	Response rate defined as >50 % change in HAM-D17	Significant improvement compared to baseline in both treatments (no placebo)	[176]

PD-MCI = Parkinson's disease with mild cognitive impairment; PDD = Parkinson's disease dementia; DLB = dementia with Lewy bodies; ADAS-Cog = cognitive subscale of the Alzheimer Disease Assessment Scale; CIBIC+ = Clinicians Interview Based Impression of Change with Caregiver input; ADCS-CGIC = Alzheimer Disease Co-operative Study Clinicians Global Impression of Change; CGIS = Clinical Global impression Scale; UPDRS = Unified Parkinson's Disease Rating Scale; BPRS = Brief psychiatric rating scale; BDI-II = Beck Depression Inventory; HAM-D17 = Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale; IDS-C = Inventory of Depressive Symptomatology-Clinician; CGI-I = Clinical Global Impression of Change; NS: not significant

disorder [12, 13]. These associated symptoms can make management of PDD even more challenging owing to coexistent psychosis and poor tolerance to medications.

The pathophysiology of cognitive impairment in PD reflects the neurochemical changes due to Lewy body pathology in cortical and brainstem regions, potentially also combined with vascular disease and AD pathology [14]. Neurochemical deficiencies of acetylcholine, dopamine, and norepinephrine have all been associated with PD-related cognitive impairment [3]. As such, approaches to managing cognitive impairment in PD have focused predominately on cholinergic agents, with some use of noradrenergic agents as well.

Pharmacologic Management of PD-MCI

To date, few studies have focused primarily on treatments for PD-MCI . Some PD patients in the early stages of the disease do report improved cognitive functioning once starting dopaminergic therapy; however, no formal studies have confirmed these anecdotal findings. As yet, there are no randomized controlled trials (RCTs) of cholinesterase inhibitors (ChEIs) for use in PD-MCI. However, a phase IV RCT of the rivastigmine transdermal patch is currently recruiting (NCT01519271) and a study of donepezil for PD-MCI and PDD is planned (NCT01014858). A pilot study of donepezil for 10 PD patients with dysexecutive alterations without dementia reported improvement [15]. Rasagiline, a monoamine oxidase-B inhibitor (MAOB-I), was examined in a study of PD patients with cognitive deficits, but not PDD, and there was improvement of some measures of attention, suggesting a positive impact on executive function [16]. A longer-term study is ongoing (NCT013823420). Another MAOB-I in development, safinamide, has been evaluated for cognitive impairment in PD, but the results of this clinical trial have not yet been reported (NCT01211587).

Poor attention has often been associated with poor cognitive function. Increasing levels of norepinephrine or dopamine have thus been suggested to improve attention and possibly cognition. The selective norepinephrine reuptake inhibitor (NRI) atomoxetine was found to improve executive dysfunction in a pilot study [17] and was also found to improve global cognitive performance in PD patients with depression, although the clinical significance was not assessed [18]. One pilot study reported significantly improved attention after administration of a single dose of the dopamine reuptake inhibitor methylphenidate, but with no change to memory or visuospatial performance [19]. However, tolerability of methylphenidate is in question as sleepiness and worsened motor function and quality of life were reported with use of this medication in one study [20], and increased heart rate and weight loss in another [21].

Pharmacologic Management of PDD

Management of PDD relies on therapies that have been developed for AD. RCTs of these medications in PD patients use outcome measures for cognition that were developed originally for AD (including AD Assessment Scale-Cognitive Assessment Subscale and AD Cooperative study-Clinicians Global Impression of Change), and thus the relevance for PDD is uncertain (Table 2).

ChEIs are frequently used to treat PDD and may have a more substantial effect owing to the greater cholinergic deficit in PDD compared with AD [22]. ChEIs as a class have a positive impact on global assessment, cognitive function, behavioral disturbance, and activities of daily living in PDD according to a 2012 Cochrane review [23]. Rivastigmine was evaluated in a DBRCT and found to moderately improve measures of dementia, cognition, and behavioral symptoms in patients with PDD [24]. Subsequent analysis of the secondary outcome measures of attention, executive function, and activities of daily living found significant improvement associated with rivastigmine use [25–27]. Similar positive findings on cognition, as well as anxiety and apathy, were demonstrated in another large RCT of rivastigmine in patients with DLB [28]. The most frequent adverse effects were nausea, vomiting, and tremor. Further examination of the effect of rivastigmine on rest tremor found that incidence was a transient phenomenon during dose titration [29]. Rivastigmine is available as a transdermal patch, which may have improved tolerability and thus cause fewer gastrointestinal symptoms than the capsule [30]. To reduce the possibility of skin reactions daily rotation is recommended. Ongoing studies are evaluating the potential benefit of the rivastigmine patch compared with the oral capsule in PDD (NCT00623103).

Improvement in cognition was found with two open-label studies of donepezil for PDD [31, 32]. However, the results of 3 small and 1 large DBRCT of donepezil for PDD were conflicting [33–36]. A trial of donepezil for DLB demonstrated significant cognitive, behavioral, and global improvement [37]. Another ChEI, galantamine, has only been evaluated for the PDD population in open-label studies, but these have also reported improvement of cognitive scores [38, 39]. Mild worsening of tremor in a small number of patients was reported in both studies.

Glutamate dysfunction has also been associated with cognitive impairment. Memantine, an *N*-methyl D-aspartate receptor antagonist used to treated moderate-to-severe AD, has been examined in the PDD population. A DBRCT of both PDD and DLB patients found benefit in the DLB group only [40]. Another RCT involving both patient groups reported significantly better clinical global impression of change, the primary outcome measure, in PDD compared with placebo [41]. The most common adverse effects in those treated with memantine were psychiatric symptoms, tiredness, and swelling. Leroi et al. [42] examined only PDD patients in an unblinded 22-week pilot study and reported a global deterioration in level of functioning 6 weeks after memantine was withdrawn.

Non-pharmacological management of cognitive impairment in PD is extremely important [43, 44]. Education and support of family and carers, including addressing power of attorney issues, are part of the management of these symptoms [45]. Limiting exposure to drugs that may potentially worsen cognitive functioning is important, such as anticholinergic agents used to treat tremor and amantadine. PD patients with dementia also frequently experience other neuropsychiatric issues such as mood disorders and psychosis (see below) that can become challenging to co-manage.

Summary

Cognitive deterioration occurs in the majority of those with PD. Studies are ongoing to determine whether ChEIs are beneficial for PD-MCI. PDD can be treated with ChEIs, with best evidence for rivastigmine.

Psychosis in PD

Psychosis in the context of PD may involve 3 main entities: minor symptoms, including illusions, sense of presence, or passage; hallucinations; and paranoid delusions. Hallucinations are most common and are present in 10–48 % of PD patients, with a lifetime prevalence at up to 60 % [46]. The most common type of hallucinations are well-formed visual images, but patients may also experience hallucinations involving other sensory modalities, including auditory, tactile, olfactory, somatic, or gustatory hallucinations [47]. Some patients also describe "minor" symptoms, including a sense of presence, hallucinations of passage, misidentification syndromes, and/or visual illusions [47]. Delusions tend to be less common, occurring in about 5 % of patients [48]. However, such symptoms tend to be the most bothersome and are associated with a loss of insight, and include paranoid delusions, often of spousal infidelity or abuse. Such symptoms can be extremely disruptive and frightening to the patient and caregivers. The quality of life of PD patients and their families and caregivers is greatly influenced by the presence of psychotic symptoms [49], and the continued presence is frequently associated with a need for institutionalization [50].

Many PD-related factors can contribute to the development of psychotic symptoms, including being older than 65 years, older age at disease onset, disease duration >6 years, more advanced disease, rapid eye movement sleep behavior disorder, impaired visual acuity, higher doses of dopamine agonists, axial parkinsonism, cognitive impairment or dementia, or a family history of dementia [51]. Conversely, early visual hallucinations are an established risk factor for early dementia [52].

Rarely, hypomania or mania may occur in PD patients following subthalamic nucleus deep brain stimulation (STN-DBS) [53]. Electrode placement (ventromedial location), unipolar stimulation, higher voltage, male sex, and early-onset PD are all associated with this outcome [53]. Pharmacological treatment may improve this psychiatric disturbance so as to preserve the motor benefits of surgical intervention [54].

The pathophysiology of visual hallucinations in PD likely involves pathological changes within cortical visual processing pathways with possible loss of higher cortical inhibitory input [55]. Pathological studies have reported increased Lewy bodies within visual areas of the temporal cortex in PD patients with visual hallucinations compared with non-hallucinators [56, 57]. Imaging studies have also shown selective changes within these regions [58, 59]. There is some evidence that dysfunction of 5HT2A receptors within the visual pathways may be associated with the development of visual hallucinations in PD patients [60].

Pharmacologic Management of Psychosis

PD medications (dopaminergic and non-dopaminergic) and many non-PD medications, as well as delirium from general medical illness, can all trigger hallucinations [61]. It is important that the effect of medications and potential concurrent illness, such as infection, be evaluated and managed. Consideration must be given to newly started medications or those where the dose has been recently increased, and reduction or discontinuation may be necessary. Regarding PD medications, anticholinergic agents and amantadine should be stopped first, and if hallucinations persist, MAOB-Is and dopamine agonists thereafter. Psychotic symptoms, however, may continue despite such measures, and management then requires specific measures.

Pharmacologic management of psychosis related to PD generally reflects treatment of psychosis in other illnesses, particularly schizophrenia, and primarily involves use of dopamine antagonists (antipsychotics/neuroleptics). However, the PD population can be challenging to manage in this respect as many antipsychotics have the potential to worsen PD motor symptoms by blocking dopamine D2 receptors. All "typical" antipsychotics and a considerable proportion of the "atypical" antipsychotics are likely to aggravate parkinsonism, and should be avoided. Specifically, there are reports of dramatic worsening of motor symptoms in PD with use of risperidone [62, 63]. Likewise, olanzapine has been found to cause significant deterioration of motor function and has failed to consistently improve hallucinations [64, 65]. Despite evidence for efficacy of ziprasidone [66], reports of worsened extrapyramidal symptoms also exist, as well as concern over prolonged QT interval [67, 68]. Aripiprazole was also recently evaluated and resulted in worsening of parkinsonism, and is not recommended for us in PD psychosis [69].

Clozapine and quetiapine, in doses markedly lower than used to treat schizophrenia, have been studied most extensively. The results of two 4-week, double-blind, placebo-controlled RCTs of clozapine with 12-week open-label extensions have been positive [70, 71] in reducing psychosis without worsening of PD motor symptoms. There is a mandatory requirement for blood monitoring for the risk of neutropenia. The results of studies on quetiapine have been mixed with respect to efficacy [72–74], although in clinical practice is more widely used owing to ease of use. Two comparison trials between clozapine and quetiapine had inconsistent results in that both supported the efficacy of clozapine, while the effectiveness of quetiapine was variable [75, 76].

Pimavanserin, a serotonin 2A receptor inverse agonist, has also been examined as a treatment for PD-related psychosis. In

a double-blind RCT of 199 PD patients with visual hallucinations treated over 43 days, preliminary reports showed efficacy in reducing visual hallucinations and no impairment of motor function [77, 78].

ChEIs may be useful in reducing visual hallucinations [79], although a RCT with such agents for this indication as not yet been conducted. In clinical practice, often starting a PD patient with dementia on a ChEI will also very effectively control visual hallucinations. There is no evidence that ChEIs will reduce paranoid delusions.

Summary

Psychoses, particularly visual hallucinations, are frequently diagnosed in PD patients and may be primary to the illness. However, secondary causes, such as infection and medication-induced psychosis, should be ruled out. Quetiapine and clozapine are beneficial for PD-related psychosis and are the neuroleptics least likely to worsen parkinsonism.

Mood Disorders in PD

Mood disorders, including depression, anxiety, and apathy, are common in PD and may precede the appearance of parkinsonian motor symptoms in some patients [80]. The "premotor" symptoms of depression and anxiety in PD are thought to relate to brainstem monoamine pathology affecting the locus coeruleus and dorsal raphe nucleus at an early stage, before the occurrence of dopamine cell loss in the substantia nigra pars compacta [81]. Depression and anxiety in later PD probably reflects multiple neurotransmitter changes. Anxiety can be a common "off-period" symptom associated with low levels of dopamine. Rarely, panic can be associated with off periods and can be a trigger for emergency room visits [82].

Mood disorders have been associated with significant morbidity and mortality [83], and are a major determinant of quality of life in individuals with PD [84]. Those with depression have a more negative emotional response to being diagnosed with PD, a more negative perception of the consequences of having PD, such as feeling obligated to withdraw or avoid previously-enjoyed activities, and a more negative subjective response to treatment [85]. Cognitive dysfunction is more common in depressed PD patients without dementia [86] and these individuals have worse scores on scales of motor function and activities of daily living [87]. Additionally, caregiver burden and distress are significantly higher when caring for a PD patient with mood-related symptoms, including depression, anxiety, apathy, and irritability[88].

While several RCTs have been performed evaluating treatments for depression in PD, none has investigated anxiety alone or apathy specifically, and, as such, there are still no strong recommendations for management of mood disorders in PD. To date, results from RCTs investigating depression and anxiety have been highly variable [89]. This relates to several issues, including small numbers of patients recruited, short treatment periods, and diversity in methods used. A wide range of endpoints, including mood-related validated questionnaires, has been utilized, which makes comparisons between studies using the same drugs challenging. Inclusion criteria have also varied, as some studies only recruited patients who satisfied the *Diagnostic and Statistical Manual of Mental Disorders* criteria for a mood disorder, while others actively excluded these patients and instead used results of questionnaires to identify and quantify the severity of mood symptoms. In general, no disease-specific drugs are available for mood disorders in PD, and management of these symptoms relies on use of antidepressants developed for general mood disorders.

Pharmacologic Management of Depression

The prevalence rate of depression in PD varies widely, from 2.7 % to 90 % [90]. A 2008 systematic review found clinically significant depressive symptoms in 35 % and major depressive disorder in 17 % of PD patients [91]. However, although depression in PD is highly prevalent, these symptoms often go unrecognized and, thus, appropriate management is not attempted. While it is important to always consider depression in this patient population, it can sometimes be a challenging diagnosis to make as motoric symptoms, such as slowness and lack of facial expression, may mask the underlying depression. PD-associated depression may have some differences from depression in the general population in terms of symptom profile (greater concentration difficulties and less reported sadness, anhedonia, feelings of guilt, and energy loss), potential comorbidities, including anxiety, apathy, cognitive changes, and sleep disorders, and chronicity [92]. Even with appropriate recognition of depression in PD, there is evidence that many patients may be inadequately treated [12, 93].

Current pharmacologic treatment of depression in PD generally reflects that of the non-PD population as it is believed the pathophysiology is similar. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) form the mainstay of treatment. However, dopaminergic cell loss in addition to serotoninergic and noradrenergic cell loss occurs in PD owing to the fundamental neurodegenerative processes of the illness [94].

Of special note, depression may develop during periods of dopamine deficiency—"off-periods" when dopaminergic medication wears off and symptoms re-emerge [95]. Because of this, it is important to address the timing of the depressive symptoms for PD patients, and in those who appear to have "off-period" depression, first try to adjust their dosing regimen to avoid the occurrence of "off-periods". This can be done by

fractionation of their current medication dosage into more frequent doses or through the addition of other medications to increase their total dopamine intake (levodopa, dopamine agonists), or prolong the effect of their current medication [catechol-O-methyltransferase inhibitors (e.g., entacapone, tolcapone) or MAOB-Is (e.g., selegiline, rasagiline)].

Dopamine agonists have been investigated for a role in the management of PD-related depression. One open-label [96] and 2 double-blind [97, 98] studies have evaluated the effect on depression separate from the known motor benefit. All three studies involved pramipexole, one compared to placebo, another to sertraline, and the open-label study to pergolide, another dopamine agonist, as add-on to levodopa therapy. In all studies pramipexole was efficacious, as was sertraline (although remission rate was higher with pramipexole), while pergolide was not. However, Leentjens [99] reviewed the data for pramipexole and argued that it was inconsistent and insufficient to demonstrate a clinically significant benefit for depressive symptoms or major depressive disorder. Given the considerable potential side effect profile of dopamine agonists, including ICDs, hallucinations, and excessive daytime sleepiness, he suggested that this therapy be tried only when depression develops with reduction or cessation of dopaminergic therapy, or in early PD when the extent to which motor dysfunction is contributing to low mood is uncertain. More recently, a post hoc analysis of RECOVER, an exploratory RCT of rotigotine, a transdermal dopamine agonist patch, for non-motor symptoms of PD, determined that this medication may improve the symptoms of depression [100].

There are few high-quality, large RCTs to date that examine the use of antidepressants for depression in PD (see Table 2 for overview). A 2013 systematic review and meta-analysis was only able to include 6 DBRCTs of antidepressants for PD-related depression [101–107]. Studies ranged from 4.5 to 12 weeks in duration, and involved sertraline [102, 106], citalopram [105, 107], paroxetine [103, 104], venlafaxine [102, 103], desipramine [107], and nortriptyline [104]. Depression was evaluated by either the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale. When all 6 studies were analyzed, there was no statistically significant superiority of antidepressants over placebo. However, in the sensitivity analysis, when low-quality studies were excluded, antidepressants were superior to placebo.

SSRIs are often used to treat PD depression because of, theoretically, fewer side effects than other classes of antidepressants. DBRCTs, however, do not show superior benefit over other medication classes, and there are no direct comparison studies between SSRIs to determine relative efficacy. A recent large DBRCT comparing venlafaxine (SNRI) and paroxetine (SNRI) suggests that SNRIs are similarly effective to SSRIs, with no difference in tolerability [103]. In RCTs, TCAs have shown superiority to SSRIs [104, 107]. Despite TCAs having potential anticholinergic side effects, such as hallucinations, cognitive impairment, and sleepiness, tolerability (specifically that of the secondary amines such as desipramine and nortriptyline) has been suggested by Skapinakis et al. [108] to be better than SSRIs. Nortriptyline appears to have a better effect in lower doses than other TCAs [109] (< 100 mg/day compared to 200–300 mg/day), which may contribute to the lack of prominent side effects in many patients. Based on all published studies up to 2013, Seppi et al. [89] concluded that nortriptyline, desipramine, and paroxetine are likely efficacious for treatment of depressive symptoms in PD, and venlafaxine is efficacious.

A small trial of mirtazapine, a presynaptic alpha-2 adrenoreceptor antagonist that increases norepinephrine and serotonin levels, reported as an abstract only, improved depression in PD patients [110]. Success with bupropion has been described in case reports only [111]. However, the unique dual norepinephrine and dopamine reuptake inhibitory action of bupropion, without the potential serotoninergic side effects (weight gain, sedation, sexual dysfunction) seen in SSRIs, SNRIs, and TCAs, may make it ideally suited to treat depressive symptoms in PD [112]. The NRI atomoxetine was evaluated in a blinded RCT, and there was no improvement in depression [18]. An open-label study of reboxetine [113], a NRI used in Europe, demonstrated improved depression scores.

Serotonin syndrome is a theoretical risk when using serotoninergic antidepressants in combination with MAOB-Is. However, the risk is much less than with non-selective MAO inhibitors, and, in practice, the incidence of serotonin syndrome is extremely rare [114]. Glutamate antagonism as an alternative treatment approach has been unsuccessful thus far; a pilot trial of the glutamate antagonist memantine for PD-associated depression did not show any benefit compared with placebo [115].

Uncontrolled studies and RCTs have demonstrated that cognitive behavioral therapy can be an effective treatment for PD depression [116–118]. Case reports have described improvement of depression in PD patients following electroconvulsive therapy [119–121].

Pharmacologic Management of Anxiety

Prevalence rates for anxiety in the PD population range from 3.6 % to 40 % [122]. Anxiety is more common in female and younger-onset PD patients, and frequently coexists with depression in some patients [122]. Many different anxiety syndromes are seen in PD, including generalized anxiety disorder, social phobia, panic disorder with and without agoraphobia, obsessive compulsive disorder, and anxiety disorder not otherwise specified [90]. Patients may also develop social anxiety secondary to having PD, such that their anxiety stems from concern about the emergence of symptoms while in a social environment. Anxiety may be present continuously, only during “off-periods”, or when transitioning from “on” to “off”.

As follows, if anxiety is related to wearing off of dopaminergic medication, it may respond to alterations in dosing regimen or addition of an adjunctive PD therapy, such as a catechol-O-methyltransferase inhibitors or MAOB-I. In addition, the use of rapid-acting subcutaneous apomorphine can be effective for off–period-related anxiety [123].

Counselling, education-based strategies, and relaxation techniques may be used to treat anxiety in PD, and, pharmacologically, anxiety is typically managed with antidepressants in a similar manner to depression, despite a lack of RCT data to support their use. Benzodiazepines also have anxiolytic properties, but they are not typically recommended for PD patients because of their potential for adverse effects such as cognitive and psychomotor impairment. The evidence-based review published by the Movement Disorders Society in 2011 [89] found insufficient evidence for the treatment of anxiety to make any recommendations.

In non-PD patients with generalized anxiety disorder, a systematic review and meta-analysis of drug treatments found fluoxetine to be most effective and sertraline most easily tolerated, although citalopram and escitalopram were not included in the analysis [124]. When anxiety was assessed as a secondary outcome in other studies on the PD population, nortriptyline was superior to placebo [104], whereas atomoxetine was not efficacious [18].

Pharmacologic Management of Apathy

Apathy is typically defined as a lack of motivation or loss of interest. In PD patients, the frequency of apathy ranges from 13.9 % to 70.0 % [125]. It is associated with poor quality of life, impaired daily functioning, medication noncompliance, and increased mortality [126, 127]. Except for more rarely reported neuropsychiatric symptoms, apathy is the symptom that most frequently causes caregiver distress in PD patients' next of kin (94.5 %) [88]. It often occurs with depression and can also coexist or even herald cognitive decline and dementia in PD [126, 128]. Higher levels of education, living in a rural environment, lower comorbidity and motor impairment, and left-onset or left-predominant PD motor laterality are all protective factors against apathy [122, 129]. Studies have reported an increase in apathy, possibly only transiently, following DBS, most commonly of the STN [130].

Similar to anxiety, there is a lack of RCTs assessing treatment of apathy in PD as a primary outcome. As a secondary outcome, however, atomoxetine was found ineffective for apathy [18]. The effect of levodopa on apathy was investigated in an open-label comparison study and motivation was shown to improve during the "on" state [131]. The post hoc analysis of the RECOVER study also found an improvement in apathy following use of the rotigotine patch for 4 weeks [100]. Ropinirole, another dopamine agonist, was used by 8 patients following STN-DBS, and a significant improvement in apathy and other mood symptoms was reported after 6 months of treatment [132]. An open-label RCT of the efficacy of continuous apomorphine infusion on neuropsychological functions including depression and apathy is currently recruiting (NCT01039090).

Summary

Mood symptoms, including depression, anxiety, and apathy, may predate the motor symptoms of PD and may occur only or worsen during "off-periods". SSRIs (paroxetine), SNRIs (venlafaxine), and TCAs (nortriptyline, despipramine) have demonstrated efficacy in DBRCTs of PD-related depression. Beyond its effect on PD motor symptoms, pramipexole has also shown benefit for depression. Anxiety may be managed successfully, but modifying dopaminergic medications to avoid "off-periods". However, to date, there is insufficient evidence to recommend other pharmacotherapy for treatment of anxiety or apathy.

Impulsive and Compulsive Behaviors in PD

Impulsive and compulsive behaviors (ICBs) have been recognized as serious and relatively common adverse effects in PD patients taking dopaminergic medication. ICBs include ICDs, dopamine dysregulation syndrome (DDS), and punding.

Management ICDs

ICDs are a heterogeneous group of gratifying behaviors that are performed to a pathological extent, most commonly pathological gambling, compulsive shopping or eating, and hypersexuality [133]. Kleptomania, hoarding, impulsive smoking, reckless generosity, reckless driving, and walkabouts, or excessive, aimless walking are also listed under the classification of ICDs [134].

In the DOMINION study, a large cross-sectional study of ICDs in PD, the 6-month prevalence of ICDs for all treated PD patients was reported to be 13.6 %, and for those on dopamine agonists, it was 17 % [135]. Thus, the greatest risk of developing an ICD is in patients taking dopamine agonists and this risk is highest during the first few months of therapy [133]. MAOB-Is have also been identified recently as a predictor of occurrence of ICDs [136]. Single status, younger age, current cigarette smoking, and a family history of addiction have all been associated with development of ICDs [135], and other risk factors include male sex, younger age at PD onset, history of substance use or bipolar disorder, and other instances of impulsive and novelty-seeking behaviors [137]. Counselling patients and their families and caregivers about the potential for developing ICDs and evaluation at regular intervals are essential. Additionally, based on the risk factors noted above, avoidance

or very cautious use of dopaminergic medication, especially dopamine agonists, with particularly close follow-up is necessary in patients at greater risk of developing ICDs. A recent study in untreated PD patients showed that ICDs may be present in up to 18.5 %, although this was not significant versus age-matched controls at 20 % [138]. However, it means that physicians planning to start a PD patient on a dopamine agonist should be aware and always ask; as patients with pre-existing ICDs are at risk of worsening with the addition of such drugs.

Management of ICDs typically involves reduction of the dopamine agonist dose, and if rapid improvement does not occur, complete discontinuation. Worsening of PD motor symptoms may develop while tapering the dopamine agonist, and simultaneous titration of levodopa may help to alleviate this, although levodopa use has also been associated with ICDs [139]. Involvement of caregivers, family, and friends to limit the patients' access to money, internet websites, food, casinos, etc., may be necessary. While dopamine agonist therapy is being withdrawn, patients may develop depression, dysphoria, anxiety, panic attacks, agoraphobia, fatigue, pain, orthostatic hypotension, and/or drug cravings. These symptoms comprise the dopamine agonist withdrawal syndrome and have been found to occur in 15–20 % of PD patients [140, 141].

Few studies have examined the pharmacologic treatment of ICDs. One double-blind crossover study involving 17 PD patients with pathological gambling found that amantadine abolished or reduced the behavior in all treated patients [142]. However, a post hoc analysis of participants in the DOMINION study (728 patients using amantadine, 2357 without amantadine use) determined that amantadine was positively associated with a diagnosis of any ICD [143], and so use of amantadine is currently controversial. In a small, open-label study, 15 patients with ICDs were treated with zonisamide, a sulphonamide analogue, (starting dose 25 mg/day, titrated as tolerated to 200 mg/day) and a marked reduction in the severity of impulsive behaviors and global impulsiveness was found without a significant change in motor function [144]. There are published case reports and retrospective reviews describing successful treatment of ICDs with donepezil [145], quetiapine [146], clozapine [147, 148], valproate [149] (risk of motor deterioration), topiramate [150], naltrexone [151], finasteride [152], cyproterone acetate [153] (for hypersexuality in a patient with PDD), and variable results with SSRIs [149, 154, 155], low-dose risperidone [156, 157], and olanzapine [149] (risk of motor deterioration with risperidone and olanzapine). A RCT of naltrexone for ICDs that showed some benefit has recently been reported in abstract form only [158]. A RCT of nicotine is currently recruiting (NCT01216904).

Management of DDS

DDS denotes the compulsive use of dopaminergic medication resulting in impairment of social or occupational functioning due to negative physical or psychiatric effects [133]. Prevalence values for DDS range from 0.6 % to 4.0 % [134] and it is usually caused by levodopa, although dopamine agonists, including subcutaneous apomorphine, have also been implicated [159]. Predictors of DDS include higher dopaminergic drug intake, greater past illicit drug use, younger age at disease onset, higher alcohol intake, depressive symptoms, and novelty-seeking personality traits [160].

Enforced gradual reduction of dopaminergic medication until a lower fixed dose is achieved is the mainstay of treatment for DDS [161]. It is recommended that any "booster" medications, such as subcutaneous apomorphine boluses and rapid-acting levodopa, be stopped completely. Cooperation of the patients' family and healthcare providers, including pharmacist, family physician, treating clinician, and/or psychiatrist, is essential, and use of blister packs and limited prescription quantities can be helpful. During dopaminergic medication reduction patients have the potential for development or worsening of psychiatric conditions, such as psychosis, hypomania, or severe depressive or anxious states. Hospital admission may be necessary for inpatient management with atypical antipsychotics, antidepressants, and/or behavioral therapy [161]. A case series also reported a positive response to valproate in four patients with DDS [162].

Management of Punding

The term "punding" refers to repetitive, complex, often purposeless, stereotyped behaviors and speech performed by some PD patients, such as sorting or disassembling common objects, cleaning, grooming, writing, playing a musical instrument, or singing [160, 163]. Punding prevalence rates range from 1.4 % to 13.8 % [134] and may co-occur with DDS [160]. These behaviors occur most frequently when levodopa and dopamine agonists are used simultaneously, but can also develop with use of only one medication class [159]. Like DDS and ICDs, management typically involves reduction of dopaminergic medications. Reversal of punding with amantadine [164] and clozapine [165] has been described in case reports, while results with antidepressants have been mixed [155, 166]. An open-label prospective study reported efficacy in controlling punding with amantadine in four cases, levodopa therapy in two cases, and mild efficacy with utilization of quetiapine in two cases [167].

From a non-pharmacologic perspective, a CBT-based intervention was shown in one study to provide significantly greater improvement than standard medical care in global ICD symptom severity and psychiatric symptoms, but not measures of carer burden and distress [168]. Some case reports have demonstrated resolution of ICBs in PD patients after STN-DBS and subsequent dopaminergic medication reduction [169, 170], but others have described new-onset ICDs or worsening of pre-existing ICDs [171, 172].

Summary

ICBs are related to use of dopaminergic medications and should be reviewed with patients on a regular basis. Reduction or complete cessation of the most likely causative agent, dopamine agonists for ICDs, levodopa for DDS, and either for punding, is the mainstay of management. Success with other pharmacologic therapies and behavioral therapy has also been reported.

Conclusion

Appropriate management of the cognitive, behavioral, and psychiatric symptoms and side effects of PD and PD medications first involves recognition. Modification or discontinuation of PD-related and non-PD medications may be necessary. There are no PD-specific pharmacologic therapies available, and in many areas there are few studies that strongly support the use of any particular therapy. Table 1 highlights the medications with the best available evidence for management of PD-related neuropsychiatric symptoms. Care must be taken to avoid using medications that may worsen PD symptoms.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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