Curr Neurol Neurosci Rep (2016) 16: 49
DOI 10.1007/s11910-016-0647-4

Neuropsychiatric Issues in Parkinson's Disease

Jeffrey W. Cooney[1] · **Mark Stacy**[2]

Published online: 5 April 2016

Abstract Cognitive and neuropsychiatric symptoms are common in Parkinson's Disease and may surpass motor symptoms as the major factors impacting patient quality of life. The symptoms may be broadly separated into those associated with the disease process and those that represent adverse effects of treatment. Symptoms attributed to the disease arise from pathologic changes within multiple brain regions and are not restricted to dysfunction in the dopaminergic system. Mood symptoms such as depression, anxiety, and apathy are common and may precede the development of motor symptoms by years, while other neuropsychiatric symptoms such as cognitive impairment, dementia, and psychosis are more common in later stages of the disease. Neuropsychiatric symptoms attributed to treatment include impulse control disorders, pathologic use of dopaminergic medications, and psychosis. This manuscript will review the current understanding of neuropsychiatric symptoms in Parkinson's Disease.

Keywords Parkinson's disease · Non-motor symptoms · Depression · Cognitive impairment · Psychosis · Impulse control disorders

This article is part of the Topical Collection on *Movement Disorders*

✉ Mark Stacy
mark.stacy@duke.edu

Jeffrey W. Cooney
jeffrey.cooney@duke.edu

[1] Duke University School of Medicine, 932 Morreene Rd., Durham, NC 27705, USA

[2] Duke University School of Medicine, 120a Davison, Durham, NC 27705, USA

Introduction

Parkinson's Disease (PD) is clinically defined by the presence of motor symptoms, including bradykinesia, rigidity, tremor, and postural instability. With time and increasing levodopa therapy, dyskinesias may also be seen. However, numerous non-motor symptoms may also arise from the disease process or may result from pharmacologic or surgical treatment. Cognitive and neuropsychiatric symptoms occur in nearly all PD patients and may surpass motor symptoms in their impact on quality of life. These symptoms arise from alpha-synuclein pathology causing dysfunction in multiple brain regions and neurochemical systems. Mood symptoms such as depression, anxiety, and apathy are common and may precede the development of motor symptoms by years, while other neuropsychiatric symptoms such as cognitive dysfunction, dementia, and psychosis are more common in later stages of the disease. The neuropsychiatric symptoms attributed to treatment of PD include impulsive and compulsive behaviors, pathologic overuse of dopaminergic medications, and psychosis. Counseling about the risks of iatrogenic impulsive and compulsive behaviors, and screening for these symptoms, are particularly important because many patients minimize these behaviors, or may not identify them as adverse effects of treatment. Optimal treatment of PD requires a comprehensive approach to the patient, including careful management of cognitive and neuropsychiatric symptoms.

Mood Symptoms in PD

Mood symptoms such as apathy, depression, and anxiety are common in PD and may precede the onset of motor symptoms by many years [1, 2]. These symptoms do not merely represent a response to the challenges of managing a chronic

disease, but are due to underlying disease pathology [3, 4]. The concept of mood symptoms as a "pre-motor" stage of PD is consistent with the neuroanatomical staging system proposed by Braak and colleagues, who demonstrated early accumulation of alpha-synuclein within brainstem structures, followed by rostral spread into the midbrain, basal ganglia, and, eventually, the cortex [5, 6]. Following this pattern, dysfunction within the dorsal raphe nucleus and locus coeruleus may disrupt serotonergic and noradrenergic systems and may occur before significant loss of dopaminergic cells within the substantia nigra results in overt motor symptoms [7, 8]. Dysfunction in the dopaminergic system also contributes to the development of mood symptoms in PD, and the symptoms may vary both with the chronic dysfunction of the system and with fluctuating serum levels of levodopa or dopamine agonists [9].

Depression in PD

Depression is the most common mood disorder in PD and is more common than in age-matched controls in other chronic diseases, such as diabetes, hypertension, coronary artery disease, or congestive heart failure [3, 4, 10–12]. A systematic review in 2015 estimated that 50–70 % of patients with PD had been affected by symptoms of depression [13••], while others report that 35 % had clinically significant depressive symptoms and 17 % met criteria for major depressive disorder [4]. The estimated prevalence of depression varies widely between studies, and depressive symptoms have been reported in up to 90 % of patients [11].

Notably, some patients experience symptoms of depression that emerge or worsen during "off" periods, when serum (and presumably brain) levels of dopaminergic medication are lower and the parkinsonian motor features are inadequately treated. Special care must therefore be taken to screen for symptoms that vary along with motor symptoms, and to adjust dopaminergic medications accordingly.

Despite the high prevalence of depression in PD, there is little evidence to guide therapy in these patients. While numerous reports of treatment of depression in PD may be found in the literature, many are limited by small sample size, short duration, design issues, or incompatible outcome measurements. In a systematic review and meta-analysis of antidepressant treatments for PD in 2015, Bomasang-Layno et al. found only 13 pharmacologic interventional trials that could be compared in a quantitative analysis [13••]. These included selective serotonin reuptake inhibitors (SSRIs: citalopram [14], sertraline [15, 16], fluoxetine [17], and paroxetine [18, 19•]), serotonin–norepinephrine reuptake inhibitors (SNRIs: venlafaxine [19•]), and tricyclic antidepressants (TCAs: desipramine [14], amitriptyline [16], nortriptyline [18], and doxepin [20]), as well as the atypical agents trazodone [21] and nefazodone [17], among medication classes typically used for treating depression. The authors also included several agents not typically used to treat these symptoms: pramipexole [22, 23], pergolide [22, 23], atomoxetine [24], and memantine [25]. Among studies included in the review, only SSRIs showed an aggregate statistically significant improvement, although the TCA group effect may have been limited by the inclusion of a study of low-dose doxepin for insomnia, with depression measured only as a secondary outcome. In contrast, studies that directly compared SSRIs with TCAs report similar efficacy for both groups, with TCAs demonstrating a more rapid onset of symptomatic improvement in some studies [14, 16–18]. Similarly, in a direct comparison of venlafaxine with paroxetine, Richard et al. found both medications to have similar effects [19•].

In addition to these agents, bupropion, a norepinephrine and dopamine reuptake inhibitor (NDRI), appears uniquely suited to treat depression in the PD population [26] and has been shown to improve both depression [27, 28] and motor symptoms in some patients [27]. However, only a very small trial and case reports are currently available to support its use, and case reports of drug-induced parkinsonism or dystonia have been associated with this agent [29, 30]; further studies are needed.

Pramipexole, a dopamine agonist, has been shown to improve symptoms of depression in comparison with sertraline [31] and with placebo [32]. The benefits of pramipexole appear to be separate from the motor improvement seen in treated patients [32]. Pergolide is of unclear benefit [22] but should not be used due to the risk of cardiac valvular fibrosis [33]. Transdermal rotigotine produced improvement in symptoms of low mood and anhedonia when compared to placebo in a post hoc analysis, but no prospective trials have been performed [34]. A 2011 review of 19 studies of dopamine agonists for depression in PD by Leentjens [35] found that as a class, dopamine agonists yielded promising but unclear results. However, given the potential for adverse effects including fatigue, impulse control disorders, hallucinations, and edema, he and others have recommended that dopamine agonists not be used as first-line therapy for depression in PD [13••, 35, 36].

Atomoxetine, an SNRI that is indicated for use in ADHD, did not improve symptoms of depression in PD but did improve daytime sleepiness and an assessment of global cognition [24]. While a small open-label study of adjunct atomoxetine for patients with refractory depression did show some improvement, this drug should be prescribed in a limited setting [37]. Methylphenidate does not improve depression in PD [38, 39], and memantine also does not appear to be beneficial for depression in PD [25].

Overall, current studies do not identify an optimal approach to treatment of depression in PD, although multiple medications do appear to be beneficial (Table 1). Selective serotonin reuptake inhibitors as a class appear to be generally effective

Table 1 Selected RCTs evaluating pharmacologic treatment of depression in PD

Category (significance)	Intervention (*n*)	Control (*n*)	Duration (weeks)	Relevant measure(s)	Significant outcomes	Study
Antidepressants:						
SSRI (*), SNRI (*)	Paroxetine (42) Venlafaxine XR (34)	Placebo (39)	12	HAM-D	Improvement with paroxetine versus placebo *and* with venlafaxine XR versus placebo. No significant differences between paroxetine and venlafaxine XR	Richard 2012
TCA (*), SSRI (NS)	Nortriptyline (17) Paroxetine CR (18)	Placebo (17)	8	HAM-D	Improvement with nortriptyline versus placebo *and* versus paroxetine CR. No significant improvement with paroxetine CR versus placebo	Menza 2009
Atypical TCA (*)	Trazodone (8)	No treatment (12)	20	HAM-D	Improvement with trazodone versus no treatment	Werneck 2009
SSRI (*), TCA (*)	Citalopram (16) Desipramine (17)	Placebo (6)	10	MADRS	Improvement with both medications versus placebo by 30 days. Improvement at 14 days with desipramine only	Devos 2008
TCA (NS),SSRI (*)	Amitriptyline (15)	Sertraline (16)	12	HAM-D, PDQ-39	Improvement with sertraline on both measures. Improvement on HAM-D but not PDQ-39 with amitriptyline	Antonini 2005
Atypical TCA (*), SSRI (*)	Nefazodone (9)	Fluoxetine (7)	12	BDI	Improvement in both groups versus baseline	Avila 2003
TCA (NS)	Doxepin (6)	Placebo (6)	6	BDI	No significant improvement (secondary measure)	Rio Romenets 2013
SSRI (NS)	Sertraline (6)	Placebo (6)	10	MADRS	No significant improvement	Leentjens 2003
SSRI (NS)	Citalopram (19)	Placebo (19)	6	HAM-D	No significant improvement	Wermuth 1998
Dopamine Agonists:						
DA (*)	Pramipexole (139)	Placebo (148)	12	BDI	Improvement with pramipexole versus placebo	Barone 2010
DA (*), DA (NS)	Pramipexole (22)	Pergolide (19)	32	MADRS, Zung	Improvement with pramipexole on both measures. Improvement on Zung but not MADRS with pergolide.	Rektorova 2003
DA (NS)	Pergolide (10) Pramipexole (10)	Placebo (10)	12	BDI, HADS	No significant improvement or differences between groups (secondary measure)	Navan 2003
Others:						
NMDAr (NS)	Memantine (20)	Placebo (20)	8	HAM-D	No significant improvement	Ondo 2011
SNRI (NS)	Atomoxetine (28)	Placebo (27)	8	IDS-C	No significant improvement	Weintraub 2010

BDI Beck Depression Inventory, *DA* dopamine agonist, *HAM-D* Hamilton Depression Rating Scale, *HADS* hospital anxiety and depression scale, *IDS-C* Inventory of Depressive Symptomatology-Clinician, *MADRS* Montgomery and Asberg Depression Rating Scale, *NMDAr* NMDA receptor antagonist, *PDQ-39* Parkinson's Disease Questionnaire-39, *SNRI* selective norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *Zung* Self-Rating Depression Scale by Zung, *NS* not significant

*Significant

and well tolerated [13••]. The SNRI venlafaxine appears to have a comparable benefit to SSRIs [19•]. The TCAs nortriptyline and desipramine have demonstrated efficacy and may have a more rapid onset of effect than SSRIs but are more likely to result in adverse effects [14, 18]. Pramipexole has demonstrated efficacy for treatment of depression in PD but is generally used as second-line therapy in patients whose motor symptoms are inadequately treated, due to the risks associated with dopamine agonists [31, 32, 35, 36].

Anxiety in PD

Anxiety is the second most common mood disorder in PD, with an estimated 40–50 % of patients experiencing clinically significant symptoms of anxiety, and approximately one third of patients meeting diagnostic criteria for an anxiety disorder [40–42]. Anxiety syndromes in PD include generalized anxiety, social phobias, specific phobias (including fear of "off" periods or freezing), and panic attacks; the symptoms are frequently co-morbid with depression [40, 41, 43]. Anxiety symptoms may be present throughout the day but are frequently encountered during "off" periods of insufficient motor control, or during the transition from "on" to "off" periods. Similar to depression, it is essential to screen for anxiety symptoms that vary with motor symptoms, and to adjust dopaminergic medications to limit or prevent off periods and motor fluctuations.

Despite the high prevalence of anxiety in PD, there are no randomized, controlled trials (RCTs) to guide treatment. A 2011 update to the Movement Disorders Society (MDS) evidence-based medicine review found insufficient evidence to make any recommendations for the treatment of anxiety in PD [33], and no significant trials have been published since that time. Treatment of anxiety in PD therefore follows the

approach to treatment of anxiety in patients without PD, and is similar to the treatment of depression. Separately, implantation of deep brain stimulation (DBS) electrodes in the subthalamic nucleus (STN) or globus pallidus pars interna (GPi) has been associated with improvement in anxiety, although STN DBS has also been associated with depression and other neuropsychiatric symptoms [44, 45]. At present, there is no clear role for the use of DBS in management of mood symptoms in PD.

Apathy in PD

Apathy is also common in patients with PD, affecting 20–40 % of patients without dementia, and up to 60 % of patients with PD and dementia after 5–10 years [46–48]. Apathy shares many symptoms with depression, including loss of interest in goal-directed behaviors and emotional blunting, but is differentiated by the relative absence of mood symptoms. Apathy is also correlated with worsening cognitive impairment and is a predictor of further cognitive decline and dementia [49, 50]. It is a major cause of caregiver distress [51].

There are limited data to guide the treatment of apathy in PD. Symptoms of co-morbid depression or dementia should be addressed, and the possibility of symptoms occurring secondary to recent reductions in levodopa or dopamine agonist therapy (especially following DBS) should be considered. Non-pharmacological treatments include the establishment of daily schedules to keep patients engaged. Pharmacologic treatment options include cholinesterase inhibitors, psychostimulants, or dopamine agonists in selected patients.

Transdermal rivastigmine (9.5 mg/day) was shown to significantly improve apathy after 6 months of treatment in a double-blind, placebo-controlled study of 31 patients with PD and moderate to severe apathy, but without dementia or depression [52]. Caregiver burden and instrumental ADLs were also improved, although overall quality of life was unchanged.

Methylphenidate has been found to be beneficial in a case report [53], and in a small group of seven patients treated with high doses of methylphenidate (1 mg/kg) for 90 days after STN DBS [54]. However, these patients were part of a larger study that was primarily assessing the effects of methylphenidate on gait. Atomoxetine was not found to improve apathy in PD patients with depression and apathy, although this was also a secondary outcome measurement [24].

Dopamine agonists may have efficacy treating apathy in PD, but the data are limited and may apply only to those patients who have undergone reduction of their dopaminergic medications and are undertreated. A double-blind, randomized, placebo-controlled trial (DBRCT) of 37 patients with PD and apathy after STN DBS surgery and medication reduction found that treatment with peribedil, a D2/D3 dopamine receptor agonist, improved scores on an apathy rating scale by 35 % in the peribedil group, versus 3 % in the placebo group after 12 weeks of treatment [55]. Similarly, an open-label study of eight patients who had stopped *all* dopaminergic therapy after STN DBS found that treatment with ropinirole was associated with improvement in apathy rating scores [56]. A post hoc analysis of transdermal rotigotine for control of motor symptoms found improvement in apathy symptoms after 4 weeks of treatment, when compared to placebo [34].

Cognitive Dysfunction and Dementia in PD

Cognitive impairment is common in PD, with up to 50 % of patients showing deficiencies in one or more cognitive areas within 5 years of diagnosis [57]. Affected domains include psychomotor speed, memory, executive function, visuospatial skills, and attention, while language appears to be less affected. For patients meeting criteria for mild cognitive impairment (MCI), more patients have symptoms in one domain than in multiple, and non-amnestic symptoms are more common than amnestic impairments [58, 59]. Most patients who develop PD-MCI will progress to dementia within 5 years [60], and over 80 % of patients surviving 20 years after diagnosis of PD will have dementia [61].

Treatment of Cognitive Dysfunction and Dementia in PD

Cognitive dysfunction in PD typically appears later in the disease and may reflect alpha-synuclein aggregation in the basal forebrain, medial temporal lobes, and cortex [5, 6, 62]. Cholinergic dysfunction is particularly implicated in the development of cognitive impairment in PD, and patients with PD dementia (PDD) exhibit greater cortical cholinergic deficits than those with Alzheimer's dementia (AD) [63]. Treatment of cognitive impairment in PD has focused on cholinergic agents, although drugs affecting the glutamate and norepinephrine systems may also be of benefit.

Among cholinesterase inhibitors, only rivastigmine has clear data to support its efficacy in improving cognitive impairment in PDD. Oral rivastigmine was shown to improve the Clinician Global Clinical Impression and scores on the cognitive subscale of the AD Assessment Scale (ADAS-cog) in a DBRCT of 541 patients with PD and mild-to-moderate dementia [64]. Secondary measurements of activities of daily living, attention, and executive function were also improved in the treatment group [64–66]. However, the incidence of nausea, vomiting, and tremor was significantly higher in the treatment group, with GI upset occurring in nearly a third of all treated patients. The use of transdermal rivastigmine significantly reduces the frequency of adverse effects, but a 76-week, open-label study of transdermal versus oral rivastigmine found the transdermal formulation to be somewhat less effective for treating dementia symptoms in patients

with a Mini Mental State Examination (MMSE) score ≤21 [67].

The benefit of rivastigmine for patients with MCI is unclear, as a small crossover study of transdermal rivastigmine in 28 patients with PD-MCI did not demonstrate any significant improvement in the primary outcome of Clinical Global Impression of Change (ADCS-CGIC), although Everyday Cognitive Battery scores did improve [68].

Donepezil also appears to improve some aspects of cognition in patients with PDD, although the data are mixed. A DBRCT of donepezil in 550 patients with PDD found improvement in only one of two co-primary endpoints, with patients receiving 10 mg of donepezil (but not 5 mg) demonstrating improvement on the Clinician Interview-Based Impression of Change plus caregiver input (CIBIC+) scale [69]. There was no significant improvement in ADAS-cog scores, but secondary outcomes including MMSE score and assessments of attention and executive function did improve with use of donepezil. The results of three small DBRCTs of donepezil in 7–22 patients with PDD yielded mixed results, with one finding improvement in both primary endpoints of CIBIC+ and MMSE [70], one with improvement in MMSE but not ADAS-cog [71], and one showing improvement in a memory subscale [72]. Several open-label studies suggest that donepezil can improve aspects of cognition in PD [73–75], but there is currently insufficient evidence to draw a firm conclusion about its efficacy in treating PDD.

Galantamine has only been evaluated for PDD in open label studies, and results are conflicting. One open-label, controlled trial of 41 patients with PDD demonstrated improvement in multiple aspects of cognition including ADAS-cog and MMSE [76], but another small open-label, uncontrolled trial of 16 patients with PDD showed only a trend toward improved MMSE [77]. A DBRCT of galantamine in patients with PD *without* dementia did not show improvement on any outcome measurements [78].

Cognitive impairment has also been associated with glutamatergic dysfunction, but studies of the NMDA-receptor antagonist memantine have yielded mixed results for patients with PDD. A DBRCT of 72 patients with PDD or dementia with Lewy bodies (DLB) found that 27 % of patients receiving memantine demonstrated a moderate or substantial improvement in their clinical global impression of change (CGIC) after 24 weeks, compared to zero patients receiving placebo [79]. Subgroup analysis demonstrated significant improvement among patients with PDD, but not DLB. Conversely, a subsequent DBRCT of memantine in 199 patients with PDD or DLB found that improvement in CGIC was evident only in patients with DLB, but not in those with PDD [80]. There is also a report of benefit from memantine in a safety study of patients with PDD, who demonstrated no cognitive improvement during treatment but had a greater global deterioration 6 weeks after discontinuing treatment [81]. Retrospective analyses of these trials have shown some additional benefits including improvement in reaction time and episodic memory [82], caregiver burden [83], quality of life [84], and survival time [85]. Overall, the data for use of memantine for cognitive dysfunction in PD remain unclear.

Several other medications have been investigated for PD patients with cognitive impairment but not dementia, with some showing limited benefit. A DBRCT of the MAO-B inhibitor rasagiline in 55 patients with PD and impairment in at least two of four cognitive domains (attention, executive function, memory, visuospatial function) showed improvement in attention scores, but not in other domains [86]. A small, open-label, pilot study of atomoxetine for cognitive impairment did find improvement in several measures of executive function [87].

Psychosis in PD

Psychosis affects more than 50 % of patients with PD at some time, and may affect up to 75 % of patients with PDD [88–90]. Psychotic symptoms are frequently caused or worsened by anticholinergic or dopaminergic treatment, particularly with dopamine agonists, but also occur in untreated PD [91, 92]. Symptoms range from mild visual distortions and the sense of "presence," to fully formed, complex hallucinations. Visual images of people or animals are the most common type of hallucination, although other sensory modalities may also be affected. Auditory hallucinations have been reported in 8 % of patients with PD psychosis (PDP), but predominant auditory symptoms such as those seen in schizophrenia are uncommon [93]. Grandiose, religious, and/or persecutory hallucinations are also rare in PDP. PD psychosis is also distinct from delirium, as the psychotic symptoms occur without significant change in baseline cognition. Delusions are less common in PD and affect a subset of 5–30 % patients [88, 90], but these fixed beliefs are often refractory to treatment. Psychotic symptoms in PD have been related to Lewy body pathology affecting the temporal lobes and causing diffuse cortical cholinergic dysfunction, and to serotonergic dysfunction with increased serotonin-2A (5HT2A) receptor binding potential in multiple areas including visual processing areas and prefrontal cortex [94].

Treatment of Psychosis in PD

Treatment of psychosis in PD (PDP) involves first ruling out medical causes such as delirium or metabolic disturbance, and removing iatrogenic causes. Anticholinergic medications should be discontinued or reduced, followed by MAO inhibitors and dopamine agonists. These medication adjustments may result in worsened control of motor symptoms, which can sometimes be addressed with careful increases in

levodopa; however, levodopa may also cause or worsen psychosis. Many patients with psychosis will therefore require the addition of other medications for control of their psychotic symptoms.

For patients with minor visual distortions or hallucinations, limited data and anecdotal experience suggest that the addition of a cholinesterase inhibitor may be sufficient to control their symptoms. While no DBRCTs have been conducted to specifically evaluate cholinesterase inhibitors for PDP, numerous open-label studies, case reports, and studies of PDD have reported improvement in psychosis after treatment with rivastigmine [95–97], donepezil [97–99], or galantamine [76, 77]. Cholinesterase inhibitors are generally not effective for delusions, or for more florid psychotic symptoms.

Patients with significant or refractory psychosis are frequently treated with antipsychotic agents. Among the antipsychotics, only clozapine has clearly demonstrated efficacy for the control of psychosis, but its use is complicated by the risk of agranulocytosis and the need for frequent blood monitoring. Two DBRCTs with 60 patients each have demonstrated substantial improvement in psychosis in patients with PDP during 4 weeks of blinded treatment with clozapine and 12 weeks of open-label follow-up, with no worsening of motor symptoms [100–102]. Some patients even demonstrated improvement in tremor. There was one case of neutropenia. The absence of declining motor symptoms may result from the unique mechanism of action for this agent, with weaker D2 affinity than other antipsychotics, and relatively greater affinity for D4, 5HT2A, and D1 receptors [103]. While clozapine appears to be significantly more effective at controlling psychosis than any other available medications, it remains rarely used due to the difficulty of frequent blood monitoring.

Quetiapine is frequently found to be helpful in clinical practice, although has limited data to support its efficacy. Several open-label trials [104–106] and one small DBRCT with 16 patients with PDP did find quetiapine to be effective [107], but three larger DBRCTs [108–110], and a fourth that also included patients with DLB and AD [111], did not report benefit. Some of these findings may be due to a relatively large improvement in symptoms within the placebo groups during the trials. Two studies directly comparing quetiapine with clozapine found the two drugs to be similar in their ability to control visual hallucinations; one showed no significant differences between the two drugs [112], while the other demonstrated similar improvements in clinical global impression scores, but found clozapine to be more effective at controlling delusions [113].

Other antipsychotics are generally not used for management of PDP due to worsening of motor symptoms and/or unclear efficacy, although several newer atypical antipsychotics have not been evaluated for this use. Ziprasidone may be effective based on limited evidence [114, 115] but has also been reported to worsen parkinsonian symptoms [116]. Olanzapine does not appear to be effective at reducing PDP and worsens motor symptoms [117–119]. Risperidone worsens motor symptoms in many patients and has a D2 receptor binding profile similar to the "typical" antipsychotics [120]. Aripiprazole also has unclear efficacy in controlling PDP and has been reported to cause severe worsening of extrapyramidal symptoms [121–123]. No clinical data currently exist to guide the use of newer antipsychotics including asenapine, iloperidone, lurasidone, or paliperidone.

In contrast to other "atypical antipsychotics," pimavanserin is a selective 5HT2A inverse agonist with no significant activity at dopamine or histamine receptors. It has been found to be effective for controlling psychotic symptoms in PD [124•]. A DBRCT of 199 patients with PDP found improvement in the PD-adapted Scale for Assessment of Positive Symptoms after 6 weeks of treatment with pimavanserin, and secondary measures including clinical global impression and assessment of caregiver burden were also improved. Motor function was unchanged, and there were no significant safety concerns [124•]. In contrast, an earlier trial of pimavanserin did not find significant improvement in psychosis, largely due to placebo effects that were carefully minimized in the final trial [125]. Such placebo effects may also have limited findings of efficacy for agents such as quetiapine. Nonetheless, if approved for use in PD patients, pimavanserin offers a promising new treatment whose receptor selectivity may avoid many of the adverse effects seen with other treatments for PDP.

Impulsive and Compulsive Behaviors in PD

Impulsive and compulsive behaviors (ICBs) are a serious and often overlooked risk of treatment for PD. Symptoms include impulse control disorders (ICDs), dopamine dysregulation syndrome (DDS), and punding. Treatment options are summarized in Table 2.

Impulse Control Disorders in PD

Impulse control disorders include pathologic gambling, compulsive buying, hyper-sexual behavior, and binge eating [126•]. Hobbyism, a compulsive over-interest in other activities such as collecting items or following sports scores, may also occur. These behaviors vary widely in severity but can have devastating financial and social consequences for patients and families. ICDs occur most frequently in patients using DAs, although they are also reported in patients using levodopa [127]. A cross-sectional study of 3090 patients with PD found that 17 % of patients using a DA demonstrated an ICD during 6 months of treatment, versus 7 % of patients not on a DA [127]. Longitudinal studies have found even higher prevalence, with nearly 40 % of patients receiving DA therapy developing an ICD during 4 years of treatment [128, 129].

Table 2 Management options for impulsive and compulsive behaviors in PD

Symptom:	DBRCT evidence:	Anecdotal evidence:	Outcomes:
ICD:	Amantadine		Reduced pathological gambling
	Naltrexone		Improvement in QUIP-RS scores, but not CGIC
		Clozapine	Reduced ICB including gambling, punding, hyper sexuality, hobbyism, and punding
		CBT	Reduced severity of ICB, but no reduction of caregiver burden
		DBS	Reduced ICB in many patients. Some de novo ICB (particularly eating) reported
		Intra-jejunal levodopa	Reduced ICB including gambling, hyper sexuality, eating, and shopping. Some de novo ICB also reported
		Topiramate	Reduced ICB including gambling, hyper sexuality, shopping, and eating
		Quetiapine	Reduced pathological gambling
DDS:	None	DBS	Reduced DDS, but de novo ICB also reported
		Intra-jejunal levodopa	Reduced DDS in some patients. Some de novo DDS also reported
		Valproic acid	Reduced DDS
Punding:	None	Amantadine	Reduced punding
		Clozapine	Reduced punding
		DBS	Reduced punding, but de novo ICB also reported
		Intra-jejunal levodopa	Reduced punding in some patients, but de novo punding in others
		Quetiapine	Reduced punding

All medication usage is off label

CBT cognitive behavioral therapy, *CGIC* clinical global impression of change, *DA* dopamine agonists, *DBS* deep brain stimulation, *DDS* dopamine dysregulation syndrome, *ICB* impulsive and compulsive behaviors, *ICD* impulse control disorders

The risk for developing ICD appears to increase with higher doses of dopaminergic medications, although they can occur even at low doses. Other risk factors include younger age, male sex, cigarette smoking, history of substance abuse, and history of impulsive behaviors [126•, 130].

The oral DAs pramipexole and ropinirole appear to impart similar risks for developing ICD, and it is unclear whether the use of extended release oral formulations decreases these risks. In contrast, a cross-sectional study of patients using oral DA versus transdermal rotigotine did find a significant reduction in ICD with rotigotine, with 42 % of patients on oral pramipexole or ropinirole meeting criteria for ICD based on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's disease Rating Scale (QUIP-RS), versus 19 % of patients on transdermal rotigotine [131]. Adjunctive use of rasagiline was also associated with an increased risk for ICD in this study, as well as in isolated case reports [132]. The role of amantadine is unclear, as although it was also associated with an increased incidence of ICD in the DOMINION study, a small RCT found it to be helpful with controlling pathological gambling [133].

Treatment of Impulse Control Disorders in PD

Reduction of dopaminergic therapy is the mainstay of treatment of ICD, although behavioral management including family counseling and actions such as temporarily restricting access to finances may also be essential. In many patients, reduction or cessation of a dopamine agonist will result in resolution of the ICD. However, reduction or withdrawal of the DA frequently results in worsening of motor symptoms, and some patients will develop a dopamine agonist withdrawal syndrome (DAWS) that makes further dose reduction difficult or impossible [134, 135]. For patients with worsening motor symptoms but not DAWS, careful increases in the dose of levodopa may be sufficient to address the motor symptoms without resumption of the ICD. For patients experiencing DAWS, attempts to reduce the dose of DA may result in profound fatigue, depression, anxiety, pain, drug craving, or other symptoms that do not improve with levodopa. In these patients, the dose of DA should be minimized as much as possible, without causing undue withdrawal symptoms. Clinical experience suggests that some patients may tolerate a very extended wean, while others may tolerate a transition to transdermal rotigotine.

Aside from reduction of dopaminergic therapy, pharmacological treatment of ICD with naltrexone and amantadine has demonstrated mixed results. A DBRCT assessing the effects of naltrexone in 50 patients with PD and an ICD did not find a significant difference in the primary outcome of clinical global impression of change after 8 weeks of treatment but did demonstrate a significant improvement in the QUIP-RS scores in those patients receiving naltrexone [136]. Chart review [137] and use in patients with ICDs without PD have yielded promising findings with naltrexone. In another RCT, amantadine (200 mg/day) was found to reduce pathological gambling in a

small, double-blind, crossover study of 17 patients with PD [133]. However, the role of amantadine in treating ICD remains unclear, as its use was also associated with an increased number of ICD cases in the DOMINION study.

The antipsychotics clozapine and quetiapine have also been reported to improve ICD in case reports and small patient series [138–140] but have limited data to support their use. Other antipsychotics are not recommended due to their worsening of motor symptoms. Topiramate [141] and antidepressants have been found helpful in case reports or small open-label studies, but the efficacy of these agents is also unclear.

Deep brain stimulation of the STN or GPi has been found to improve ICD in multiple studies [142–144], including in a recent prospective study of 13 patients with PD and ICD who had full resolution of symptoms 3 years after implantation [145]. However, a small number of patients have also experienced worsening or new-onset compulsive behaviors (particularly compulsive eating) after DBS [126•, 146]. The use of intra-jejunal levodopa suggested promising improvement in ICD in a small study of eight patients [147], but further studies are needed.

Dopamine Dysregulation Syndrome and Punding in PD

Dopamine dysregulation syndrome (DDS), also referred to as hedonic homeostatic dysregulation, refers to the compulsive over-use of dopaminergic medications. It is most frequently seen with levodopa but can also occur with short-acting, high-potency DAs such as subcutaneous apomorphine [126•]. Data on the prevalence of DDS are limited, but chart review from specialty centers suggests that it may occur in as many as 3–4 % of treated patients [148]. Risk factors include younger age of PD onset, depressive symptoms, higher doses of dopaminergic medications, novelty seeking personality traits, and greater alcohol use [149]. Patients with DDS exhibit symptoms often seen in other states of drug addiction, including craving, covert use of medications, hoarding of medications, and dysphoria and irritability associated with decreased use. Increased use of dopaminergic medications in DDS may result in symptoms of mania, psychosis, severe dyskinesias, or punding [126•, 149, 150].

Punding refers to repetitive, purposeless behaviors such as arranging, assembling, disassembling, or collecting objects [151]. Punding is on the spectrum of compulsive behaviors with hobbyism but consists of lower-level behaviors with less apparent goal orientation. Other similar behaviors include hoarding and "walk-abouts," consisting of aimless wandering [126•, 152]. Punding was initially described in chronic amphetamine users but, in PD, is associated with the use of high doses of dopaminergic therapy. It is most commonly seen with concomitant use of dopamine agonists and levodopa but can occur with monotherapy.

Treatment of Dopamine Dysregulation Syndrome and Punding in PD

As with other ICBs, reduction of dopaminergic therapy is central to the treatment of DDS, punding, and related behaviors. Limiting access to medications is frequently necessary, and coordination between family members, pharmacies, and other health care providers may be required to prevent covert use [36, 153••]. Conversion to intra-jejunal levodopa has been reported to improve ICD including DDS [147, 150]. However, DDS has also been reported as a complication of jejunal levodopa [154, 155].

Successful treatment of DDS with valproate has been reported in five patients, using 250–1000 mg of extended release valproate at bedtime [156, 157]. Improvement of punding after treatment with amantadine, quetiapine, and clozapine has also been reported in case reports [140, 158, 159]. Cognitive behavioral therapy was found to reduce the severity of ICBs in a study of 45 patients, although caregiver burden was not significantly improved [160].

Deep brain stimulation has enabled marked improvement in DDS and punding in multiple studies, although as mentioned above, a small number of new-onset ICBs have also been reported to occur after DBS [142–144, 146, 150, 161]. Implantation into the STN often allows substantial postoperative reduction in dopaminergic medications, although there have been no direct comparisons of STN vs. GPi DBS for management of DDS. While the current literature may not support the presence of ICD as the primary indication for DBS implantation [162], this approach may be helpful in selected patients.

Conclusion

Neuropsychiatric symptoms affect nearly all patients with PD, and optimal management of the disease requires careful attention to both motor and non-motor symptoms. Patients should be screened for mood disorders, cognitive impairment, psychosis, and compulsive behaviors, and detailed counseling about the risks of medical and surgical treatments should be provided. Screening and counseling for impulsive and compulsive behaviors are particularly important, as many patients minimize these behaviors or may not identify them as adverse affects of their medical treatment. Careful adjustment of medications, addition of pharmacologic treatments when needed, counseling, and appropriate surgical intervention will enable patients with PD to attain optimal control of a challenging and multifaceted illness.

Compliance with Ethical Standards

Conflict of Interest Jeffrey W. Cooney declares that he has no conflict of interest.

Mark Stacy works for Duke University, and has received consultancy fees from Eli Lilly, Merz, Osmotica, Pfizer, SK Life Sciences, Allergan, Avid, Best Doctors, Biotie, Lundbeck, Neuronova, Novartis Pharma (Japan), Saraepta Therapeutics, and Sunovion Pharmaceutics, Inc. Dr. Stacy has also received grants from the Michael J. Fox Foundation, the NIH, the Parkinson Study Group, and Pharma 2B, royalties from Informa Press for the Handbook of Dystonia and Duke University for the Wearing Off Questionnaire. He has also recieved payment for development of educational presentations from the University of Kansas, the University of Miami, and the University of Rochester. Dr. Stacy also received paid travel accommodations from the Cleveland Clinic Neurological Institute, the Movement Disorder Society, and the National Parkinson Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord. 2015;30(2):229–37.
2. Postuma RB, Aarsland D, Barone P, et al. Identifying prodromal Parkinson's disease: pre-motor disorders in Parkinson's disease. Mov Disord. 2012;27(5):617–26.
3. Gallagher DA, Schrag A. Psychosis, apathy, depression and anxiety in Parkinson's disease. Neurobiol Dis. 2012;46(3):581–9.
4. Reijnders JS, Ehrt U, Weber WE, et al. A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord. 2008;23(2):183–9.
5. Braak H, Del Tredici K. Neuroanatomy and pathology of sporadic Parkinson's disease. Adv Anat Embryol Cell Biol. 2009;201:1–119.
6. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24(2):197–211.
7. Espay AJ, LeWitt PA, Kaufmann H. Norepinephrine deficiency in Parkinson's disease: the case for noradrenergic enhancement. Mov Disord. 2014;29(14):1710–9.
8. Lim SY, Fox SH, Lang AE. Overview of the extranigral aspects of Parkinson disease. Arch Neurol. 2009;66(2):167–72.
9. Storch A, Schneider CB, Wolz M, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology. 2013;80(9):800–9.
10. Nuti A, Ceravolo R, Piccinni A, et al. Psychiatric comorbidity in a population of Parkinson's disease patients. Eur J Neurol. 2004;11(5):315–20.
11. Tan LC. Mood disorders in Parkinson's disease. Parkinsonism Relat Disord. 2012;18 Suppl 1:S74–6.
12. Egede LE. Major depression in individuals with chronic medical disorders: prevalence, correlates and association with health resource utilization, lost productivity and functional disability. Gen Hosp Psychiatry. 2007;29(5):409–16.
13. •• Bomasang-Layno E, Fadlon I, Murray AN, et al. Antidepressive treatments for Parkinson's disease: A systematic review and meta-analysis. Parkinsonism Relat Disord. 2015;21(8):833–42. **This review provides a quantitative meta-analysis of randomized, controlled trials for treatment of depression in PD. It includes evaluation of drug categories, evaluation ofeffect sizes, and critical assessment of the included articles**.
14. Devos D, Dujardin K, Poirot I, et al. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord. 2008;23(6):850–7.
15. Leentjens AF, Vreeling FW, Luijckx GJ, et al. SSRIs in the treatment of depression in Parkinson's disease. Int J Geriatr Psychiatry. 2003;18(6):552–4.
16. Antonini A, Tesei S, Zecchinelli A, et al. Randomized study of sertraline and low-dose amitriptyline in patients with Parkinson's disease and depression: effect on quality of life. Mov Disord. 2006;21(8):1119–22.
17. Avila A, Cardona X, Martin-Baranera M, et al. Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial. J Clin Psychopharmacol. 2003;23(5):509–13.
18. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 2009;72(10):886–92.
19. • Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology. 2012;78(16):1229–36. **This study demonstrates efficacy of an SSRI and SNRI vs placebo in treating depression in PD**.
20. Rios Romenets S. L. Creti, C. Fichten, et al., Doxepin and cognitive behavioural therapy for insomnia in patients with Parkinson's disease—a randomized study. Parkinsonism Relat Disord. 2013;19(7):670–5.
21. Werneck AL, Rosso AL, Vincent MB. The use of an antagonist 5-HT2a/c for depression and motor function in Parkinson's disease. Arq Neuropsiquiatr. 2009;67(2B):407–12.
22. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol. 2003;10(4):399–406.
23. Navan P, Findley LJ, Jeffs JA, et al. Randomized, double-blind, 3-month parallel study of the effects of pramipexole, pergolide, and placebo on Parkinsonian tremor. Mov Disord. 2003;18(11):1324–31.
24. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology. 2010;75(5):448–55.
25. Ondo WG, Shinawi L, Davidson A, et al. Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial. Parkinsonism Relat Disord. 2011;17(3):156–9.
26. Raskin S, Durst R. Bupropion as the treatment of choice in depression associated with Parkinson's disease and it's various treatments. Med Hypotheses. 2010;75(6):544–6.
27. Goetz CG, Tanner CM, Klawans HL. Bupropion in Parkinson's disease. Neurology. 1984;34(8):1092–4.
28. Zaluska M, Dyduch A. Bupropion in the treatment of depression in Parkinson's disease. Int Psychogeriatr. 2011;23(2):325–7.
29. Grandas F, Lopez-Manzanares L. Bupropion-induced parkinsonism. Mov Disord. 2007;22(12):1830–1.
30. Cheng WC, Liu CM, Hsieh MH, et al. Bupropion-related parkinsonism and dystonia. J Clin Psychopharmacol. 2009;29(6):616–8.
31. Barone P, Scarzella L, Marconi R, et al. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: a

national multicenter parallel-group randomized study. J Neurol. 2006;253(5):601–7.
32. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010;9(6):573–80.
33. Seppi K, Weintraub D, Coelho M, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011;26 Suppl 3:S42–80.
34. Ray Chaudhuri K. P. Martinez-Martin, A. Antonini, et al., Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. Parkinsonism Relat Disord. 2013;19(7):660–5.
35. Leentjens AF. The role of dopamine agonists in the treatment of depression in patients with Parkinson's disease: a systematic review. Drugs. 2011;71(3):273–86.
36. Connolly B, Fox SH. Treatment of cognitive, psychiatric, and affective disorders associated with Parkinson's disease. Neurotherapeutics. 2014;11(1):78–91.
37. Carpenter LL, Milosavljevic N, Schecter JM, et al. Augmentation with open-label atomoxetine for partial or nonresponse to antidepressants. J Clin Psychiatry. 2005;66(10):1234–8.
38. Cantello R, Aguggia M, Gilli M, et al. Major depression in Parkinson's disease and the mood response to intravenous methylphenidate: possible role of the "hedonic" dopamine synapse. J Neurol Neurosurg Psychiatry. 1989;52(6):724–31.
39. Nutt JG, Carter JH, Sexton GJ. The dopamine transporter: importance in Parkinson's disease. Ann Neurol. 2004;55(6):766–73.
40. Leentjens AF, Dujardin K, Marsh L, et al. Symptomatology and markers of anxiety disorders in Parkinson's disease: a cross-sectional study. Mov Disord. 2011;26(3):484–92.
41. Prediger RD, Matheus FC, Schwarzbold ML, et al. Anxiety in Parkinson's disease: a critical review of experimental and clinical studies. Neuropharmacology. 2012;62(1):115–24.
42. Rutten S, Ghielen I, Vriend C, et al. Anxiety in Parkinson's disease: Symptom dimensions and overlap with depression and autonomic failure. Parkinsonism Relat Disord. 2015;21(3):189–93.
43. Dissanayaka NN, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. Mov Disord. 2010;25(7):838–45.
44. Couto MI, Monteiro A, Oliveira A, et al. Depression and anxiety following deep brain stimulation in Parkinson's disease: systematic review and meta-analysis. Acta Med Port. 2014;27(3):372–82.
45. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol. 2008;7(7):605–14.
46. Dujardin K, Sockeel P, Devos D, et al. Characteristics of apathy in Parkinson's disease. Mov Disord. 2007;22(6):778–84.
47. Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, et al. Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. Mov Disord. 2008;23(13):1889–96.
48. Pagonabarraga J, Kulisevsky J, Strafella AP, et al. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol. 2015;14(5):518–31.
49. Butterfield LC, Cimino CR, Oelke LE, et al. The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. Neuropsychology. 2010;24(6):721–30.
50. Dujardin K, Sockeel P, Delliaux M, et al. Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord. 2009;24(16):2391–7.
51. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ, et al. Neuropsychiatric symptoms and caregiver's burden in Parkinson's disease. Parkinsonism Relat Disord. 2015;21(6):629–34.
52. Devos D, Moreau C, Maltete D, et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. J Neurol Neurosurg Psychiatry. 2014;85(6):668–74.
53. Chatterjee A, Fahn S. Methylphenidate treats apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci. 2002;14(4):461–2.
54. Moreau C, Delval A, Defebvre L, et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: amulticentre, parallel, randomised, placebo-controlled trial. Lancet Neurol. 2012;11(7):589–96.
55. Thobois S, Lhommee E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain. 2013;136(Pt 5):1568–77.
56. Czernecki V, Schupbach M, Yaici S, et al. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. Mov Disord. 2008;23(7):964–9.
57. Broeders M, Velseboer DC, de Bie R, et al. Cognitive change in newly-diagnosed patients with Parkinson's disease: a 5-year follow-up study. J Int Neuropsychol Soc. 2013;19(6):695–708.
58. Goldman JG, Litvan I. Mild cognitive impairment in Parkinson's disease. Minerva Med. 2011;102(6):441–59.
59. Litvan I, Aarsland D, Adler CH, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord. 2011;26(10):1814–24.
60. Pigott K, Rick J, Xie SX, et al. Longitudinal study of normal cognition in Parkinson disease. Neurology. 2015;85(15):1276–82.
61. Hely MA, Reid WG, Adena MA, et al. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23(6):837–44.
62. Dickson DW, Fujishiro H, Orr C, et al. Neuropathology of non-motor features of Parkinson disease. Parkinsonism Relat Disord. 2009;15 Suppl 3:S1–5.
63. Bohnen NI, Kaufer DI, Ivanco LS, et al. Cortical cholinergic function is more severely affected in parkinsonian dementia than in Alzheimer disease: an in vivo positron emission tomographic study. Arch Neurol. 2003;60(12):1745–8.
64. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med. 2004;351(24):2509–18.
65. Olin JT, Aarsland D, Meng X. Rivastigmine in the treatment of dementia associated with Parkinson's disease: effects on activities of daily living. Dement Geriatr Cogn Disord. 2010;29(6):510–5.
66. Schmitt FA, Farlow MR, Meng X, et al. Efficacy of rivastigmine on executive function in patients with Parkinson's disease dementia. CNS Neurosci Ther. 2010;16(6):330–6.
67. Emre M, Poewe W, De Deyn PP, et al. Long-term safety of rivastigmine in parkinson disease dementia: an open-label, randomized study. Clin Neuropharmacol. 2014;37(1):9–16.
68. Mamikonyan E, Xie SX, Melvin E, et al. Rivastigmine for mild cognitive impairment in Parkinson disease: a placebo-controlled study. Mov Disord. 2015;30(7):912–8.
69. Dubois B, Tolosa E, Katzenschlager R, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord. 2012;27(10):1230–8.
70. Aarsland D, Laake K, Larsen JP, et al. Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. J Neurol Neurosurg Psychiatry. 2002;72(6):708–12.
71. Ravina B, Putt M, Siderowf A, et al. Donepezil for dementia in Parkinson's disease: arandomised, double blind, placebo controlled, crossover study. J Neurol Neurosurg Psychiatry. 2005;76(7):934–9.
72. Leroi I, Brandt J, Reich SG, et al. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. Int J Geriatr Psychiatry. 2004;19(1):1–8.

73. Muller T, Welnic J, Fuchs G, et al. The DONPAD-study–treatment of dementia in patients with Parkinson's disease with donepezil. J Neural Transm Suppl. 2006;71:27–30.
74. Rowan E, McKeith IG, Saxby BK, et al. Effects of donepezil on central processing speed and attentional measures in Parkinson's disease with dementia and dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2007;23(3):161–7.
75. Thomas AJ, Burn DJ, Rowan EN, et al. A comparison of the efficacy of donepezil in Parkinson's disease with dementia and dementia with Lewy bodies. Int J Geriatr Psychiatry. 2005;20(10):938–44.
76. Litvinenko IV, Odinak MM, Mogil'naya VI, et al. Efficacy and safety of galantamine (reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). Neurosci Behav Physiol. 2008;38(9):937–45.
77. Aarsland D, Hutchinson M, Larsen JP. Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. Int J Geriatr Psychiatry. 2003;18(10):937–41.
78. Grace J, Amick MM, Friedman JH. A double-blind comparison of galantamine hydrobromide ER and placebo in Parkinson disease. J Neurol Neurosurg Psychiatry. 2009;80(1):18–23.
79. Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson'sdisease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. Lancet Neurol. 2009;8(7):613–8.
80. Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2010;9(10):969–77.
81. Leroi I, Overshott R, Byrne EJ, et al. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. Mov Disord. 2009;24(8):1217–21.
82. Wesnes KA, Aarsland D, Ballard C, et al. Memantine improves attention and episodic memory in Parkinson's disease dementia and dementia with Lewy bodies. Int J Geriatr Psychiatry. 2015;30(1):46–54.
83. Leroi I, Atkinson R, Overshott R. Memantine improves goal attainment and reduces caregiver burden in Parkinson's disease with dementia. Int J Geriatr Psychiatry. 2014;29(9):899–905.
84. Larsson V, Engedal K, Aarsland D, et al. Quality of life and the effect of memantine in dementia with lewy bodies and Parkinson's disease dementia. Dement Geriatr Cogn Disord. 2011;32(4):227–34.
85. Stubendorff K, Larsson V, Ballard C, et al. Treatment effect of memantine on survival in dementia with Lewy bodies and Parkinson's disease with dementia: a prospective study. BMJ Open. 2014;4(7):e005158.
86. Hanagasi HA, Gurvit H, Unsalan P, et al. The effects of rasagiline on cognitive deficits in Parkinson's disease patients without dementia: a randomized, double-blind, placebo-controlled, multicenter study. Mov Disord. 2011;26(10):1851–8.
87. Marsh L, Biglan K, Gerstenhaber M, et al. Atomoxetine for the treatment of executive dysfunction in Parkinson's disease: a pilot open-label study. Mov Disord. 2009;24(2):277–82.
88. Fenelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. J Neurol Sci. 2010;289(1–2):12–7.
89. Hely MA, Morris JG, Reid WG, et al. Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord. 2005;20(2):190–9.
90. Aarsland D, Ballard C, Larsen JP, et al. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. Int J Geriatr Psychiatry. 2001;16(5):528–36.
91. Pagonabarraga J, Martinez-Horta S, Fernández de Bobadilla R, et al., Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. Mov Disord. 2016;31(1):45–52.
92. Fenelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. Neurology. 2006;66(1):93–8.
93. Inzelberg R, Kipervasser S, Korczyn AD. Auditory hallucinations in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1998;64(4):533–5.
94. Ballanger B, Strafella AP, van Eimeren T, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. Arch Neurol. 2010;67(4):416–21.
95. Oh YS, Kim JS, Lee PH. Effect of Rivastigmine on Behavioral and Psychiatric Symptoms of Parkinson's Disease Dementia. J Mov Disord. 2015;8(2):98–102.
96. Bullock R, Cameron A. Rivastigmine for the treatment of dementia and visual hallucinations associated with Parkinson's disease: a case series. Curr Med Res Opin. 2002;18(5):258–64.
97. Sobow T. Parkinson's disease-related visual hallucinations unresponsive to atypical antipsychotics treated with cholinesterase inhibitors: a case series. Neurol Neurochir Pol. 2007;41(3):276–9.
98. Fabbrini G, Barbanti P, Aurilia C, et al. Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. Neurol Sci. 2002;23(1):41–3.
99. Kurita A, Ochiai Y, Kono Y, et al. The beneficial effect of donepezil on visual hallucinations in three patients with Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16(3):184–8.
100. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. N Engl J Med. 1999. 340(10): p. 757–63.
101. Factor SA, Friedman JH, Lannon MC, et al. Clozapine for the treatment of drug-induced psychosis in Parkinson's disease: results of the 12 week open label extension in the PSYCLOPS trial. Mov Disord. 2001;16(1):135–9.
102. Pollak P, Tison F, Rascol O, et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry. 2004;75(5):689–95.
103. Tauscher J, Hussain T, Agid O, et al. Equivalent occupancy of dopamine D1 and D2 receptors with clozapine: differentiation from other atypical antipsychotics. Am J Psychiatry. 2004;161(9):1620–5.
104. Dewey Jr RB. and P.E. O'Suilleabhain, Treatment of drug-induced psychosis with quetiapine and clozapine in Parkinson's disease. Neurology. 2000;55(11):1753–4.
105. Fernandez HH, Friedman JH, Jacques C, et al. Quetiapine for the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord. 1999;14(3):484–7.
106. Targum SD, Abbott JL. Efficacy of quetiapine in Parkinson's patients with psychosis. J Clin Psychopharmacol. 2000;20(1):54–60.
107. Fernandez HH, Okun MS, Rodriguez RL, et al. Quetiapine improves visual hallucinations in Parkinson disease but not through normalization of sleep architecture: results from a double-blind clinical-polysomnography study. Int J Neurosci. 2009;119(12):2196–205.
108. Ondo WG, Tintner R, Voung KD, et al. Double-blind, placebo-controlled, unforced titration parallel trial of quetiapine for dopaminergic-induced hallucinations in Parkinson's disease. Mov Disord. 2005;20(8):958–63.
109. Rabey JM, Prokhorov T, Miniovitz A, et al. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. Mov Disord. 2007;22(3):313–8.
110. Shotbolt P, Samuel M, Fox C, et al. A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. Neuropsychiatr Dis Treat. 2009;5:327–32.

111. Kurlan R, Cummings J, Raman R, et al. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. Neurology. 2007;68(17):1356–63.
112. Morgante L, Epifanio A, Spina E, et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27(4):153–6.
113. Merims D, Balas M, Peretz C, et al. Rater-blinded, prospective comparison: quetiapine versus clozapine for Parkinson's disease psychosis. Clin Neuropharmacol. 2006;29(6):331–7.
114. Pintor L, Valldeoriola F, Bailles E, et al. Ziprasidone versus clozapine in the treatment of psychotic symptoms in Parkinson disease: a randomized open clinical trial. Clin Neuropharmacol. 2012;35(2):61–6.
115. Gomez-Esteban JC, Zarranz JJ, Velasco F, et al. Use of ziprasidone in parkinsonian patients with psychosis. Clin Neuropharmacol. 2005;28(3):111–4.
116. Schindehutte J, Trenkwalder C. Treatment of drug-induced psychosis in Parkinson's disease with ziprasidone can induce severe dose-dependent off-periods and pathological laughing. Clin Neurol Neurosurg. 2007;109(2):188–91.
117. Breier A, Sutton VK, Feldman PD, et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. Biol Psychiatry. 2002;52(5):438–45.
118. Goetz CG, Blasucci LM, Leurgans S, et al. Olanzapine and clozapine: comparative effects on motor function in hallucinating PD patients. Neurology. 2000;55(6):789–94.
119. Ondo WG, Levy JK, Vuong KD, et al. Olanzapine treatment for dopaminergic-induced hallucinations. Mov Disord. 2002;17(5):1031–5.
120. Factor SA, Molho ES, Friedman JH. Risperidone and Parkinson's disease. Mov Disord. 2002;17(1):221–2.
121. Fernandez HH, Trieschmann ME, Friedman JH. Aripiprazole for drug-induced psychosis in Parkinson disease: preliminary experience. Clin Neuropharmacol. 2004;27(1):4–5.
122. Friedman JH, Berman RM, Goetz CG, et al. Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. Mov Disord. 2006;21(12):2078–81.
123. Wickremaratchi M, Morris HR, Ali IM. Aripiprazole associated with severe exacerbation of Parkinson's disease. Mov Disord. 2006;21(9):1538–9.
124.• Cummings J, Isaacson S, Mills R, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383(9916):533–40. **This study demonstrates efficacy of a novel agent for treating psychosis in Parkinson's disease, without dopamine blockade or worsening of motor symptoms**.
125. Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of parkinson's disease psychosis. Neuropsychopharmacology. 2010;35(4):881–92.
126.• Weintraub D, David AS, Evans AH, et al. Clinical spectrum of impulse control disorders in Parkinson's disease. Mov Disord. 2015;30(2):121–7. **This manuscript reviews the range of symptoms comprising impulse control disorders, including pathological gambling, buying, sexual behaviors, and dopamine dysregulation syndrome**.
127. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. Arch Neurol. 2010;67(5):589–95.
128. Bastiaens J, Dorfman BJ, Christos PJ, et al. Prospective cohort study of impulse control disorders in Parkinson's disease. Mov Disord. 2013;28(3):327–33.
129. Hassan A, Bower JH, Kumar N, et al. Dopamine agonist-triggered pathological behaviors: surveillance in the PD clinic reveals high frequencies. Parkinsonism Relat Disord. 2011;17(4):260–4.
130. Ceravolo R, Frosini D, Rossi C, et al. Impulse control disorders in Parkinson's disease: definition, epidemiology, risk factors, neurobiology and management. Parkinsonism Relat Disord. 2009;15 Suppl 4:S111–5.
131. Garcia-Ruiz PJ, Martinez Castrillo JC, Alonso-Canovas A, et al. Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. J Neurol Neurosurg Psychiatry. 2014;85(8):840–4.
132. Vitale C, Santangelo G, Erro R, et al. Impulse control disorders induced by rasagiline as adjunctive therapy for Parkinson's disease: report of 2 cases. Parkinsonism Relat Disord. 2013;19(4):483–4.
133. Thomas A, Bonanni L, Gambi F, et al. Pathological gambling in Parkinson disease is reduced by amantadine. Ann Neurol. 2010;68(3):400–4.
134. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. Arch Neurol. 2010;67(1):58–63.
135. Pondal M, Marras C, Miyasaki J, et al. Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. J Neurol Neurosurg Psychiatry. 2013;84(2):130–5.
136. Papay K, Xie SX, Stern M, et al. Naltrexone for impulse control disorders in Parkinson disease: a placebo-controlled study. Neurology. 2014;83(9):826–33.
137. Liang JW, Shanker VL, Groves M. Naltrexone for impulse control disorders in Parkinson disease: a placebo-controlled study. Neurology. 2015;84(13):1386–7.
138. Rotondo A, Bosco D, Plastino M, et al. Clozapine for medication-related pathological gambling in Parkinson disease. Mov Disord. 2010;25(12):1994–5.
139. Sevincok L, Akoglu A, Akyol A. Quetiapine in a case with Parkinson disease and pathological gambling. J Clin Psychopharmacol. 2007;27(1):107–8.
140. Hardwick A, Ward H, Hassan A, et al. Clozapine as a potential treatment for refractory impulsive, compulsive, and punding behaviors in Parkinson's disease. Neurocase. 2013;19(6):587–91.
141. Bermejo PE. Topiramate in managing impulse control disorders in Parkinson's disease. Parkinsonism Relat Disord. 2008;14(5):448–9.
142. Kim YE, Kim HJ, Kim HJ, et al. Impulse control and related behaviors after bilateral subthalamic stimulation in patients with Parkinson's disease. J Clin Neurosci. 2013;20(7):964–9.
143. Lhommee E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. Brain. 2012;135(Pt 5):1463–77.
144. Moum SJ, Price CC, Limotai N, et al. Effects of STN and GPi deep brain stimulation on impulse control disorders and dopamine dysregulation syndrome. PLoS One. 2012;7(1):e29768.
145. Amami P, Dekker I, Piacentini S, et al. Impulse control behaviours in patients with Parkinson's disease after subthalamic deep brain stimulation: de novo cases and 3-year follow-up. J Neurol Neurosurg Psychiatry. 2015;86(5):562–4.
146. Broen M, Duits A, Visser-Vandewalle V, et al. Impulse control and related disorders in Parkinson's disease patients treated with bilateral subthalamic nucleus stimulation: a review. Parkinsonism Relat Disord. 2011;17(6):413–7.
147. Catalan MJ, de Pablo-Fernandez E, Villanueva C, et al. Levodopa infusion improves impulsivity and dopamine dysregulation syndrome in Parkinson's disease. Mov Disord. 2013;28(14):2007–10.
148. Pezzella FR, Colosimo C, Vanacore N, et al. Prevalence and clinical features of hedonistic homeostatic dysregulation in Parkinson's disease. Mov Disord. 2005;20(1):77–81.
149. Evans AH, Lawrence AD, Potts J, et al. Factors influencing susceptibility to compulsive dopaminergic drug use in Parkinson disease. Neurology. 2005;65(10):1570–4.
150. Cilia R, Siri C, Canesi M, et al. Dopamine dysregulation syndrome in Parkinson's disease: from clinical and neuropsychological

characterisation to management and long-term outcome. J Neurol Neurosurg Psychiatry. 2014;85(3):311–8.
151. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. Mov Disord. 2004;19(4):397–405.
152. O'Sullivan SS, Djamshidian A, Evans AH, et al. Excessive hoarding in Parkinson's disease. Mov Disord. 2010;25(8):1026–33.
153.•• Samuel M, Rodriguez-Oroz M, Antonini A, et al. Management of impulse control disorders in Parkinson's disease: Controversies and future approaches. Mov Disord. 2015;30(2):150–9. **This review provides a critical assessment of management options for impulse control disorders in PD**.
154. Salomone G, Marano M, di Biase L, et al. Dopamine dysregulation syndrome and punding in levodopa-carbidopa intestinal gel (LCIG) infusion: A serious but preventable complication. Parkinsonism Relat Disord. 2015;21(9):1124–5.
155. Solla P, Cannas A, Marrosu MG et al. Dopamine dysregulation syndrome in Parkinson's disease patients on levodopa-carbidopa intestinal gel. Parkinsonism Relat Disord. 2015;21(11):1383–4.
156. Sriram A, Ward HE, Hassan A, et al. Valproate as a treatment for dopamine dysregulation syndrome (DDS) in Parkinson's disease. J Neurol. 2013;260(2):521–7.
157. Epstein J, Madiedo CJ, Lai L, et al. Successful treatment of dopamine dysregulation syndrome with valproic acid. J Neuropsychiatry Clin Neurosci. 2014;26(3):E3.
158. Fasano A, Ricciardi L, Pettorruso M, et al. Management of punding in Parkinson's disease: an open-label prospective study. J Neurol. 2011;258(4):656–60.
159. Kashihara K, Imamura T. Amantadine may reverse punding in Parkinson's disease-observation in a patient. Mov Disord. 2008;23(1):129–30.
160. Okai D, Askey-Jones S, Samuel M, et al. Trial of CBT for impulse control behaviors affecting Parkinson patients and their caregivers. Neurology. 2013;80(9):792–9.
161. Eusebio A, Witjas T, Cohen J, et al. Subthalamic nucleus stimulation and compulsive use of dopaminergic medication in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2013;84(8):868–74.
162. Okun MS, Weintraub D. Should impulse control disorders and dopamine dysregulation syndrome be indications for deep brain stimulation and intestinal levodopa? Mov Disord. 2013;28(14):1915–9.