



Published in final edited form as:

*Mov Disord.* 2011 May ; 26(6): 1022–1031. doi:10.1002/mds.23664.

## Parkinson's Disease: The Quintessential Neuropsychiatric Disorder

Daniel Weintraub, MD<sup>1,2,\*</sup> and David J. Burn, MD<sup>3,4</sup>

<sup>1</sup>Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA

<sup>2</sup>Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA

<sup>3</sup>Institute for Ageing and Health, Newcastle University, Newcastle upon Tyne, United Kingdom

<sup>4</sup>Newcastle University Clinical Ageing Research Unit, Campus for Ageing and Vitality, Newcastle upon Tyne, United Kingdom

### Abstract

Although diagnosed by characteristic motor features, Parkinson's disease may be preceded, and is frequently accompanied by, a wide range of cognitive and neuropsychiatric features. In addition to the most commonly studied disorders of dementia, depression, and psychosis, other relatively common and clinically significant psychiatric complications include impulse control disorders, anxiety symptoms, disorders of sleep and wakefulness, and apathy. These problems may be underrecognized and are frequently undertreated. The emergent focus on nonmotor aspects of Parkinson's disease over the past quarter of a century is highlighted by a nonlinear increase in the number of articles published devoted to this topic. Although the development of newer antidepressants, atypical antipsychotics, and cholinesterase inhibitors in recent years has had a positive benefit on the management of these troublesome and distressing symptoms, responses are frequently suboptimal, and this remains an area of major unmet therapeutic need.

### Keywords

Parkinson's; dementia; neuropsychiatric; depression; psychosis

---

In the first year of publication of *Movement Disorders* (1986), none of the 4 issues contained primary articles that pertained to the psychiatric and cognitive complications of Parkinson's disease (PD). The nonmotor features of PD received scant attention at that time, although there was an appreciation, present since James Parkinson's legendary quote about the melancholic features of his defining case, that depression was a common complication of PD. In addition, ever since the mid-1960s, when levodopa was introduced as the first dopamine replacement therapy (DRT) for PD, numerous studies have documented the occurrence of psychotic symptoms, particularly visual hallucinations, in treated PD patients. In general, it was thought that the “senses” were mainly preserved in PD, in part because the shortened life span of PD patients at that time precluded the development of dementia. When dementia did occur, it was considered by most to represent the co-occurrence of

---

© 2011 Movement Disorder Society

\*Correspondence to: Daniel Weintraub, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; daniel.weintraub@uphs.upenn.edu.

**Relevant conflicts of interest/financial disclosures:** Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Alzheimer's disease (AD). Other psychiatric and cognitive complications in PD either were not commonly recognized or were not frequent because of the limited prevailing treatment options available. Beyond a very limited understanding of the epidemiology of these disorders, there was also very little research conducted on assessment and diagnosis, impact and course, neuropathophysiology, or treatment. It is fair to summarize that in 1986, PD was conceptualized as predominantly a motor disorder.

## Advances in Past 25 Years

Fast forwarding 25 years, although PD is still considered a movement disorder and is diagnosed on that basis, the high prevalence of cognitive impairment and numerous psychiatric complications suggests that it is more accurately conceptualized as a neurocognitive-psychiatric disorder. In addition to the most commonly studied disorders of dementia, depression, and psychosis, other relatively common and clinically significant psychiatric complications include impulse control disorders (ICDs), anxiety symptoms, disorders of sleep and wakefulness, and apathy. The emergent focus on nonmotor aspects of PD over the past quarter of a century is exemplified by the nonlinear increase in the number of published articles devoted to this topic (Fig. 1), as well as by quality improvement efforts that increasingly stress nonmotor features.<sup>1</sup>

## Cognitive Impairment and Dementia

Significant advances in our understanding of the epidemiology of cognitive impairment in PD have been recognition that: (1) impairments occur in a range of cognitive domains, including executive, memory, visuospatial, attentional, and language functions<sup>2-6</sup>; (2) dementia (PDD) is a common long-term outcome, affecting up to 80% of patients<sup>7</sup>; (3) approximately 25% of nondemented (PD-ND) patients have mild cognitive impairment (PD-MCI),<sup>5</sup> with PD-MCI patients at increased risk of developing PDD<sup>8</sup>; and (4) a significant percentage of newly diagnosed PD patients have cognitive deficits<sup>9,10</sup> and experience cognitive decline over a several-year period.<sup>11</sup> In addition, a range of correlates and potential risk factors for cognitive decline have emerged, including increasing age and duration of PD, male sex, “atypical” parkinsonian features, and a range of other nonmotor symptoms (eg, visual hallucinations, apathy, depression, and rapid eye movement [REM] sleep behavior disorder).<sup>12-18</sup> Although coverage of the cognitive and neuropsychiatric features of dementia with Lewy bodies (DLB) is beyond the scope of this review, another major change over the past decade has been the emergence of DLB as a distinct clinical syndrome.

There has been significant expansion in research examining the neural substrate of dementia in PD. Some of the emerging conclusions to be drawn from this diverse research include: (1) diffuse subcortical Lewy body disease pathology appears to be the major contributing pathology to cognitive decline in PD<sup>19-21</sup>; (2) in addition, a significant percentage of PD patients also have AD-related neuropathological changes at autopsy,<sup>22</sup> and AD CSF biomarkers are associated with cognitive impairment and decline in PD<sup>23</sup>; (3) a range of neurotransmitter deficits are associated with cognitive impairment, including acetylcholine,<sup>24</sup> dopamine,<sup>25-27</sup> and norepinephrine<sup>28</sup>; (4) impairments in the corticostriatal neural circuitry likely contribute to cognitive impairment in PD<sup>29</sup>; (5) a range of genetic influences for specific cognitive impairments or decline have been identified, including brain-derived neurotrophic factor val<sup>66</sup>met,<sup>30</sup> catechol-O-methyl-transfer-ase val<sup>158</sup>met,<sup>31</sup> and microtubule-associated protein tau polymorphisms<sup>17</sup>; and (6) diffuse (primarily medial temporal lobe, parietal lobe, and prefrontal cortex) gray and white matter neurodegeneration<sup>32-35</sup> and metabolic deficits are associated with cognitive decline.<sup>36,37</sup> It may be that “one size does *not* fit all” in terms of the etiological basis of PDD and that

pathological and neurochemical heterogeneity underpins the observed diverse clinical presentations and therapeutic responsiveness.

A major step forward has been a Movement Disorder Society (MDS) task force, which proposed clinical criteria for the diagnosis of PDD<sup>38</sup> and published an algorithm for diagnosing PDD.<sup>39</sup> This has led to significant improvements in the validity and reliability of the diagnosis of PDD. In parallel work, several cognitive assessment instruments for different purposes have now been validated for use in PD, including the Parkinson's Disease–Cognitive Rating Scale,<sup>40</sup> the Parkinson Neuropsychometric Dementia Assessment,<sup>41</sup> the Scales for Outcomes of Parkinson's Disease–Cognition,<sup>42</sup> the Dementia Rating Scale–2, and the Montreal Cognitive Assessment.<sup>43</sup>

The management of PDD has undoubtedly benefited from “transferable treatment strategies” from the AD field. Despite this, only 1 large controlled cholinesterase inhibitor (ChEI) study in PDD has been published and represents a landmark trial in this field.<sup>44</sup> Statistically significant but clinically modest effects for rivastigmine on a range of primary and secondary outcome measures were observed, and ChEI treatment appears well tolerated overall in PD. In 2 recent controlled studies that included both PDD and DLB patients, memantine (an NMDA receptor antagonist) was found to be beneficial for PDD in one<sup>45</sup> but not the other.<sup>46</sup>

## Depression

Although “melancholy” has long been considered a frequent accompaniment of PD, the past 25 years have seen major advances in characterizing the frequency, clinical phenotype, and diagnosis of the mood disorder. Instead of considering depressed PD (dPD) patients as a homogenous group, recent epidemiological research has reported that the frequency of major (ie, more severe) depression is 5%–20%, with nonmajor forms of depression (ie, minor or subsyndromal depression) occurring in an additional 10%–30% of patients.<sup>47–50</sup> Another advance is our understanding of numerous correlates or possible risk factors for dPD, including female sex,<sup>48</sup> a personal<sup>51</sup> or family<sup>52</sup> history of depression, early-onset PD,<sup>53</sup> “atypical” parkinsonism,<sup>49</sup> and psychiatric comorbidity (eg, worse cognition, psychosis, anxiety, apathy, fatigue, and insomnia<sup>48,54–57</sup>). There is inconsistent evidence that dPD is distinct from non-PD depression, with some studies reporting higher rates of anxiety, pessimism, suicide ideation without suicidal behavior, and less guilt and self-reproach.<sup>58</sup> Not surprisingly, core non-somatic symptoms of depression discriminate most highly between depressed and nondepressed (ie, less likelihood of symptom overlap).<sup>59</sup> It has almost become dogma that suicide is uncommon in PD,<sup>60</sup> yet recent research challenges this and suggests that both death and suicidal ideation may be relatively common.<sup>61</sup>

Depression in PD likely results from a complex interaction of psychological and neurobiological factors. Supporting the latter contribution are the findings that PD patients may have more depression than other similarly disabled patients,<sup>62</sup> that there is an association between severity of depression and PD,<sup>63,64</sup> and that depression may be a prodromal syndrome in some PD patients.<sup>65,66</sup> Biologically, the high frequency of dPD has been explained by dysfunction in: (1) subcortical nuclei and the prefrontal cortex (PFC); (2) striatal-thalamic-PFC circuits and the basotemporal limbic circuit; and (3) brain stem monoamine and indolamine (ie, dopamine, serotonin, and norepinephrine) systems.<sup>36,67–74</sup>

A recent MDS task force reviewed and made recommendations for the use of depression rating scales in PD.<sup>75</sup> In addition, an NINDS/NIMH work group suggested provisional diagnostic criteria for dPD.<sup>76</sup> Hopefully, such efforts over time will help address that dPD is underrecognized and undertreated,<sup>77</sup> even in specialty care settings.<sup>78,79</sup>

Up to 25% of PD patients are now on an antidepressant at any given time, most commonly a selective serotonin reuptake inhibitor (SSRI),<sup>79,80</sup> for which clinical experience and open-label studies suggest good tolerability. Relatively few controlled antidepressant studies for dPD have been published. Interestingly, tricyclic antidepressants (TCAs) have been found to be superior to placebo,<sup>81,82</sup> but only 1 of 3 controlled SSRI studies reporting positive findings, although sample sizes were small.<sup>81,83,84</sup> In addition to traditional antidepressants, a range of other treatments recently explored for dPD in controlled studies include: (1) pramipexole (a dopamine agonist), which was found to be efficacious<sup>85</sup>; (2) atomoxetine (a selective norepinephrine reuptake inhibitor [NRI]), which was not efficacious for depression but was associated with improvement in global cognitive performance and daytime sleepiness<sup>86</sup>; (3) left PFC repetitive transcranial magnetic stimulation (rTMS), which was efficacious<sup>87</sup>; and (4) omega-3 fatty acid (ie, fish oil), which was efficacious.<sup>88</sup> Finally, psychotherapy is increasingly being explored as a treatment of dPD,<sup>89,90</sup> a positive development, given that many PD patients with depression may prefer psychotherapy, do not respond to pharmacotherapy, or are reluctant to take another medication.<sup>91</sup> The lack of randomized trial data to better inform our management of dPD remains a source of frustration, and reasons for this are multi-factorial (eg, complexity of trial design, validated end points, confounding influences from motor disability and concomitant medications, and sources of funding). One can only hope that the next 25 years sees more dramatic advances in this area.

## Psychosis

Although psychosis (PD-P) occurs in fewer than 10% of untreated PD patients and was uncommon prior to the introduction of DRT,<sup>92</sup> a recent prospective study that encompassed currently available treatments reported a long-term cumulative prevalence of 60%.<sup>93</sup> Visual hallucinations are most commonly reported in PD, but auditory, tactile, and olfactory hallucinations are also relatively common.<sup>94</sup> The overwhelming majority of PD-P patients also report disturbances of sleep and wakefulness, including REM behavior disorder (RBD)<sup>95,96</sup>; other correlates or risk factors are exposure to PD medications,<sup>97</sup> older age,<sup>55</sup> and greater cognitive impairment.<sup>56</sup>

Despite the association between medication exposure and PD-P, the dosage and duration of antiparkinsonian treatment do not clearly correlate with psychosis,<sup>55,98</sup> indicating that the etiology of PD-P is complex. One proposed mechanism is that chronic DRT may lead to excessive stimulation or hypersensitivity of mesocorticolimbic D<sub>2</sub>/D<sub>3</sub> receptors<sup>99</sup>. Cholinergic deficits and a serotonergic/dopaminergic imbalance using a range of imaging modalities and other neural probes have also been implicated,<sup>99–101</sup> particularly in the primary visual system and dorsal/ventral visual association pathways.<sup>102–106</sup> Finally, neurodegeneration of widespread limbic, paralimbic, and neocortical gray matter, including the PFC, is associated with PD-P.<sup>107,108</sup>

A recent MDS task force reviewed psychosis rating scales used in PD and listed 4 instruments as “recommended” for use in PD as outcome measures in clinical trials,<sup>109</sup> and an ongoing MDS Task Force is developing and validating a new psychosis rating scale for PD.

Management of PD-P is complex. Observational research suggests that management of comorbid medical conditions and discontinuation or decreasing dosages of nonessential medications may be sufficient for many patients, at least in the short term.<sup>110</sup> Medications are usually discontinued sequentially and gradually (anticholinergics, selegiline, amantadine, DAs, catechol-O-methyltransferase inhibitors, and finally, a reduction in levodopa dosage), although this strategy is not evidence based.<sup>111</sup> The past 25 years has seen something of a “rise and fall” of atypical antipsychotics (APs), as a number of unforeseen safety issues

emerged in the context of their use in elderly demented patients. In PD-P, several theoretically promising atypical agents, such as risperidone, olanzapine, and most recently aripiprazole, have been tried and then failed as adverse events, primarily worsening extrapyramidal signs, have precluded their routine prescription. Currently quetiapine is the most commonly used AP, despite the fact that all controlled clinical trials with reasonable sample sizes have been negative or uninterpretable.<sup>112–114</sup> Two notable randomized clinical trials showed that clozapine is efficacious for PD-P,<sup>115,116</sup> yet the drug is rarely used because of the requirement for routine blood monitoring. A recent controlled study of pimavanserin, a serotonin<sub>2A</sub> receptor inverse agonist with a promising receptor binding profile, was negative,<sup>117</sup> although the unexpectedly large placebo effect in this trial has encouraged further studies of this agent.

### Impulse Control Disorders and Related Behaviors

The topic of impulse control disorders and related behaviors has been something of a “growth industry” in PD over the past decade, coinciding with the introduction of D2-selective dopamine agonists (DAs). It is fascinating to observe how these disorders were first reported as a sporadic occurrence and then characterized epidemiologically and phenomenologically in detail. Impulse control disorders (ICDs; ie, compulsive gambling, buying, sexual behavior, and eating) are now known to occur relatively commonly in PD.<sup>118</sup> As patients may not report such behaviors to a treating physician, either because of embarrassment and not suspecting an association with PD treatment or ambivalence regarding ceasing the behavior or treatment, ICDs remain generally underrecognized in clinical practice.<sup>119</sup>

In a recent large multisite observational study, an ICD was identified in 14% of PD patients, and 4% had comorbid ICDs.<sup>120</sup> ICDs were more common in patients taking a DA. Both levodopa<sup>120</sup> and amantadine<sup>121</sup> use were also associated with ICDs, although to a lesser extent than was DA treatment. A personal or familial history of alcoholism or gambling, impulsive or novelty-seeking characteristics, young age, male sex, and early PD onset<sup>118</sup> have emerged as additional correlates or risk factors associated with ICD in PD.

Dopamine dysregulation syndrome (ie, DDS or compulsive PD medication use) and other impulsive-compulsive disorders in PD have also been recognized, but not as well studied.<sup>122</sup> Punding (ie, repetitive, non-goal-directed activity) was reported in 14% of PD patients on higher levodopa dosages in 1 study,<sup>123</sup> but another larger study of unselected PD patients reported a frequency < 2%.<sup>124</sup>

A range of cognitive impairments have been reported in PD ICD patients, most commonly executive deficits, including impulsive decision-making.<sup>125–127</sup> The dopamine system has been implicated, with both ICD and DDS patients having sensitized D<sub>2</sub>/D<sub>3</sub> receptors,<sup>128,129</sup> and decreased dopamine transporter availability in ICD patients.<sup>130</sup> Functional imaging studies have reported altered striatal activation and corticostriatal connectivity in ICD patients.<sup>131,132</sup>

ICD behaviors often resolve after discontinuing DA treatment.<sup>133</sup> However, many patients do not want or tolerate DA discontinuation, and a DA withdrawal syndrome (DAWS) was recently described.<sup>134</sup> The relationship between deep brain stimulation (DBS) and ICDs is complex. Subthalamic nucleus (STN) DBS has been associated with improvement in ICD symptoms,<sup>135</sup> but there is also anecdotal evidence that ICDs may begin or worsen transiently post-DBS surgery.<sup>136</sup> A range of psychiatric treatments (eg, SSRIs and APs) have been used to treat ICDs in PD, but there is no empirical evidence to support their use in PD patients. A recent small controlled study reported benefit for amantadine as a treatment for pathological gambling in PD.<sup>137</sup>

## Disorders of Sleep and Wakefulness

Remarkably, disorders of sleep and wakefulness have emerged over the past 25 years as perhaps the most common nonmotor complications of PD, with up to 90% of patients reporting insomnia, hypersomnia, sleep fragmentation, sleep terrors, nightmares, nocturnal movements, or RBD.<sup>138,139</sup> RBD, along with impaired olfaction and depression/anxiety, may be a key clinical feature of the important nonmotor prodrome of PD.<sup>140</sup> Other sleep cycle-related disorders that occur in PD are restless legs syndrome (RLS), periodic leg movements in sleep (PLMS), and obstructive or central apnea.<sup>138</sup> RBD and other sleep disturbances have been attributed both to progressive degeneration of the cholinergic pedunculopontine nucleus (PPN)<sup>141</sup> and reduced striatal dopaminergic activity.<sup>142</sup> Associated clinical factors that can disrupt sleep in PD patients are parkinsonism, autonomic symptoms, and psychiatric/cognitive disorders.<sup>12,138,143</sup>

Excessive daytime sleepiness (EDS) and fatigue (physical or mental) are common in PD,<sup>144,145</sup> but the relationship between the 2 has not been fully delineated. EDS has been attributed variably to impairments in the striatal-thalamic-frontal cortical system, exposure to DRT (especially DAs), and nocturnal sleep disturbances.<sup>138,143</sup> As with RBD, psychiatric comorbidity<sup>144,146</sup> is frequently concurrent with EDS and fatigue. Daytime “sleep attacks” (ie, sudden-onset REM sleep) were first reported toward the end of the last century and were initially attributed to DA treatment, although recent thinking suggests they may actually be a manifestation of EDS.<sup>147</sup>

Treatment of sleep disturbance depends on the underlying etiology and includes adjustment to PD medications (for PD-related sleep disturbances, RLS, and PLMS) and clonazepam (for RBD). Regarding psychotropic medication, melatonin may improve subjective sleep disturbance in PD,<sup>148,149</sup> and a controlled trial of eszopiclone (a nonbenzodiazepine hypnotic) was partially positive.<sup>150</sup> Evidence has been mixed for modafinil<sup>151–154</sup> and psychostimulants<sup>155</sup> as treatments for EDS and fatigue.

## Complications of Deep Brain Stimulation Surgery

Over the past decade DBS has been used increasingly as a treatment for PD, and despite many studies, its impact on nonmotor symptoms appears to be varied and complex.<sup>156,157</sup> A recent meta-analysis<sup>158</sup> and 2 controlled studies of DBS versus best medical therapy (BMT)<sup>159,160</sup> identified significant declines post-DBS in executive functions and verbal learning and memory, not surprising given that DBS electrodes course through the PFC and subcortical white matter when implanted. The use of model-based stimulation parameters to minimize the spread of current to non-motor portions of the STN reverses the cognitive decline that occurred post-DBS,<sup>161</sup> suggesting that post-DBS cognitive decline may be preventable. Psychiatric findings post-DBS have included both overall improvement and occasionally worsening of depression, anxiety, psychosis, mania, apathy, and emotional lability.<sup>156</sup> In controlled DBS studies, there were no between-group differences in mood post-DBS surgery,<sup>160,162</sup> and 1 study reported improvement in anxiety symptoms with DBS.<sup>159</sup> Interestingly, in 1 controlled study comparing STN with globus pallidus interna (GPi) DBS, patients who received STN DBS were more likely to experience worsening in both depressive symptoms and processing speed.<sup>163</sup> Clinically, pre- and post-DBS psychiatric and cognitive monitoring are important, especially given reports of postsurgical suicide ideation and completed or attempted suicide.<sup>164</sup>

## Nonmotor Fluctuations

Although motor fluctuations (MFs) have long been recognized as a complication of DRT, only recently has research demonstrated that the majority of patients with MFs also experience nonmotor fluctuations (NMFs), including anxiety, slowness of thinking, fatigue,

and dysphoria. Furthermore, NMFs are often the more disabling of these complications.<sup>165</sup> The relationship between motor status and NMFs is complex, as there is not always a correlation between affect and motor state,<sup>166,167</sup> and improvements in mood post-levodopa infusion in patients with MFs can precede improvements in motor status.<sup>168</sup> It remains to be seen if treatments shown to reduce severity or duration of MFs also lead to improvements in severity or duration of NMFs.

### Other Disorders of Affect

Compared with depression, both anxiety and apathy in PD have received scant attention to date. Up to 40% of PD patients experience anxiety symptoms or disorders, including generalized anxiety disorder (GAD), panic attacks, and social phobia.<sup>169–172</sup> Increasing anxiety and discrete anxiety attacks have been associated with NMFs, particularly the onset of “off” periods.<sup>171,172</sup> Similar to depression, there is an increased frequency of anxiety disorders up to 20 years prior to PD onset,<sup>173,174</sup> but other than this clue, little is known about the etiology of anxiety in PD. There have been no controlled anxiety treatment studies in PD, but antidepressant treatment studies have reported secondary benefit for anxiety symptoms. For patients who experience anxiety as part of an “off” state, PD medication adjustments can be made in an attempt to decrease the duration and severity of these episodes. However, many patients require treatment with benzodiazepines, although this medication class must be used cautiously in PD patients because of their propensity to increase sedation, gait imbalance, and cognitive impairment.

Apathy occurs in approximately 40% of PD patients<sup>175,176</sup> and can occur independently of depression and cognitive impairment, although overlap is common.<sup>175,177</sup> Studies of apathy in PD have reported associations with executive deficits, verbal memory impairment, and bradyphrenia,<sup>175,178</sup> with decreased cingulate and inferior frontal gyri volumes.<sup>179</sup> There have been no treatment studies for apathy in PD, but in 1 observational study, apathy that developed post-DBS surgery responded to DA treatment.<sup>180</sup>

### Global Neuropsychiatric

A recent trend in neuropsychiatric research has been to focus on global neuropsychiatric symptoms (NPSs) and to use advanced statistical techniques to delineate neuropsychiatric profiles in PD to help account for the substantial comorbidity and interindividual heterogeneity that occurs. For instance, in 1 study that used latent class analysis in a cohort of mild–moderate PD patients, 3 of the 4 classes delineated experienced significant but different patterns of cognitive and psychiatric symptoms and comprised more than two thirds of patients.<sup>181</sup> In another study using factor analysis, the first and strongest of 4 factors included cognitive impairment, psychotic symptoms, depression, and EDS.<sup>182</sup>

Recently, several global assessment instruments have been developed and tested for clinical use in PD, including the Non-Motor Symptoms Scale<sup>183</sup> and the Scales for Outcomes in Parkinson's Disease–Psychiatric Complications.<sup>184</sup> In addition, the Neuropsychiatric Inventory<sup>185</sup> is commonly used in PD to document the presence and severity of a range of NPSs, and the MDS-UPDRS has an expanded Part I that queries about cognitive symptoms and numerous NPSs.

### Where We Stand and Future Directions

To summarize advances over the past 25 years and the current state of affairs, numerous overarching themes emerge: (1) longitudinal studies have demonstrated that the cumulative prevalence of most psychiatric and cognitive complications is much higher than previously thought, with many disorders having a cumulative frequency well over 50%; (2) ample research has documented that nonmotor complications of PD are associated to varying

degrees with excess disability, worse QoL, poorer outcomes, and caregiver burden, which highlight their clinical significance as an independent area of clinical focus and research; (3) there have been significant advances in the number of validated screening instruments and rating scales, as well as consensus diagnostic criteria for many psychiatric and cognitive disorders, which has led to improved clinical management and higher-quality research; (4) although our understanding remains limited, there is mounting evidence that the neural substrate of nonmotor complications in PD is a complex interaction of strategically placed PD and other neuro-degenerative disease pathology, deficits in multiple neurotransmitters, impairments in neural circuitry sub-serving mental functioning, and poorly elucidated genetic influences; (5) core PD treatments, especially DRT and DBS, have a complex and varied effect on psychiatric symptoms and cognitive abilities, in certain instances being an etiological factor and in others offering a treatment option; and (6) despite the advances highlighted above, current treatment options for the range of disorders discussed generally remain limited, and nearly all drugs were developed or first used for similar conditions in non-PD patients.

Additional research is needed to address the incomplete understanding of the epidemiology, phenomenology, risk factors, neuropathophysiology, and optimal management strategies for all the discussed disorders. Despite the advances made in the past 25 years, only 7 of the 107 “citation classics” in PD relate to psychiatric or cognitive complications, with almost all focusing on cognitive deficits.<sup>186</sup> High-priority areas for future research include: (1) conducting long-term, longitudinal epidemiological research focused on the predictors, development, course, and impact of cognitive decline and psychiatric disorders; (2) using sophisticated statistical techniques to reconceptualize the classification of psychiatric and cognitive disorders in PD to account for the significant comorbidity, heterogeneity, and variability in symptoms that occur and to generate novel pathophysiological hypotheses; (3) improving recognition and diagnosis through continued development and validation of diagnostic criteria and clinically useful assessment tools that are specific to PD; (4) improving our understanding of the neural substrate of cognitive and psychiatric complications through examination of neuropathology, disease-specific biomarkers, neurotransmitters, brain structure, and neural circuitry; (5) resolving the DLB versus PDD debate, as the overlap between DLB and PDD is extensive, and additional research and expert consensus is needed to determine if separate diagnostic categories for these 2 disorders are viable; and (6) conducting large-scale clinical trials to determine the efficacy of different interventions for different psychiatric and cognitive complications, including the use of disease-modifying agents (when available) to delay or prevent cognitive and psychiatric complications. Ultimately, reducing the impact of PD on patients and families will require improved recognition and the development of better therapies for its nonmotor complications.

## References

1. Cheng EM, Tonn S, Swain-Eng R, et al. Quality improvement in neurology: AAN Parkinson disease quality measures: report of the Quality Measurement and Reporting Subcommittee of the American Academy of Neurology. *Neurology*. 2010; 75:2021–2027. [PubMed: 21115958]
2. Dujardin K, Degreef JF, Rogelet P, Defbvre L, Destee A. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. *J Neurol*. 1999; 246:783–788. [PubMed: 10525975]
3. Cronin-Golomb A, Braun AE. Visuospatial dysfunction and problem solving in Parkinson's disease. *Neuropsychology*. 1997; 11:44–52. [PubMed: 9055268]
4. Lewis SJG, Cools R, Robbins TW, Dove A, Barker RA, Owen AM. Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease. *Neuropsychologia*. 2003; 41:645–654. [PubMed: 12591022]



5. Aarsland D, Bronnick K, Williams-Gray CH, et al. Mild cognitive impairment in Parkinson's disease: a multicentre pooled analysis. *Neurology*. 2010; 75:1062–1069. [PubMed: 20855849]
6. Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Stern MB. Evidence for both impaired encoding and retrieval memory profiles in Parkinson's disease. *Cogn Behav Neurol*. 2004; 17:195–200. [PubMed: 15622014]
7. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol*. 2003; 60:387–392. [PubMed: 12633150]
8. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. *Mov Disord*. 2006; 21:1343–1349. [PubMed: 16721732]
9. Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. *Eur J Neurol*. 2009; 16:1278–1284. [PubMed: 19538208]
10. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G, ParkWest Study Group. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest Study. *Neurology*. 2009; 72:1121–1126. [PubMed: 19020293]
11. Kandiah N, Narasimhalu K, Lau P-N, Seah S-H, Au WL, Tan LCS. Cognitive decline in early Parkinson's disease. *Mov Disord*. 2009; 24:605–616. [PubMed: 19191342]
12. Vendette M, Gagnon J-F, Dècary A, et al. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology*. 2007; 69:1843–1849. [PubMed: 17984452]
13. Tomer R, Levin BE, Weiner WJ. Side of onset of motor symptoms influences cognition in Parkinson's disease. *Ann Neurol*. 1993; 34:579–584. [PubMed: 8215246]
14. Green J, McDonald WM, Vitek JL, et al. Cognitive impairments in advanced PD without dementia. *Neurology*. 2002; 59:1320–1324. [PubMed: 12427877]
15. Aarsland D, Andersen K, Larsen JP, Lolk A, Nieman H, Kragh-Sorensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. *Neurology*. 2001; 56:730–736. [PubMed: 11274306]
16. Uc EY, McDermott MP, Marder KS, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. *Neurology*. 2009; 73:1469–1477. [PubMed: 19884574]
17. Williams-Gray CH, Evans JR, Goris A, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. *Brain*. 2009; 132:2958–2969. [PubMed: 19812213]
18. Starkstein SE, Mayberg HS, Leiguarda R, et al. A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1992; 55:377–382. [PubMed: 1602311]
19. Hurtig HI, Trojanowski JQ, Galvin J, et al. Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. *Neurology*. 2000; 54:1916–1921. [PubMed: 10822429]
20. Kovari E, Gold G, Herrmann FR, et al. Lewy body densities in the entorhinal and anterior cingulate cortex predict cognitive deficits in Parkinson's disease. *Acta Neuropathol (Berl)*. 2003; 106:83–88. [PubMed: 12687392]
21. Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. *Ann Neurol*. 2005; 58:773–776. [PubMed: 16240351]
22. Jellinger KA, Seppi K, Wenning GK, et al. Impact of coexistent Alzheimer pathology on the natural history of Parkinson's disease. *J Neural Transm*. 2002; 109:329–339. [PubMed: 11956955]
23. Siderowf A, Xie SX, Hurtig H, et al. CSF amyloid {beta} 1–42 predicts cognitive decline in Parkinson's disease. *Neurology*. 2010; 75:1055–1061. [PubMed: 20720189]
24. Bohnen NI, Albin RL. Cholinergic denervation occurs early in Parkinson's disease. *Neurology*. 2010; 73:256–257. [PubMed: 19535769]
25. Kaasinen V, Rinne JO. Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. *Neurosci Biobehav Rev*. 2002; 26:785–793. [PubMed: 12470690]

26. Rinne JO, Portin R, Ruottinen H, et al. Cognitive impairment and the brain dopaminergic system in Parkinson disease. *Arch Neurol*. 2000; 57:470–475. [PubMed: 10768619]
27. Müller U, Wächter T, Barthel H, Reuter M, von Cramon Y. Striatal [<sup>123</sup>I]beta-CIT SPECT and prefrontal cognitive functions in Parkinson's disease. *J Neural Transm*. 2000; 107:303–319. [PubMed: 10821439]
28. Zweig RM, Cardillo JE, Cohen M, Giere S, Hedreen JC. The locus ceruleus and dementia in Parkinson's disease. *Neurology*. 1993; 43:986. [PubMed: 8492957]
29. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex*. 2001; 11:1136–1143. [PubMed: 11709484]
30. Foltynie T, Lewis SGJ, Goldberg TE, et al. The BDNF Val<sup>66</sup>Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. *J Neurol*. 2005; 252:833–838. [PubMed: 15772739]
31. Williams-Gray CH, Hampshire A, Barker RA, Owen AM. Attentional control in Parkinson's disease is dependent on COMT val<sup>158</sup>met genotype. *Brain*. 2008; 131:397–408. [PubMed: 18178571]
32. Kenny ER, Burton EJ, O'Brien JT. A volumetric magnetic resonance imaging study of entorhinal cortex volume in dementia with Lewy bodies. A comparison with Alzheimer's disease and Parkinson's disease with and without dementia. *Dement Geriatr Cogn Disord*. 2008; 26:218–225. [PubMed: 18781072]
33. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. *Brain*. 2004; 127:791–800. [PubMed: 14749292]
34. Gattellaro G, Minati L, Grisoli M, et al. White matter involvement in idiopathic Parkinson disease: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2009; 30:1222–1226. [PubMed: 19342541]
35. Karagulle Kendi AT, Lehericy S, Luciana M, Ugurbil K, Tuite P. Altered diffusion in the frontal lobe in Parkinson disease. *AJNR Am J Neuroradiol*. 2008; 29:501–505. [PubMed: 18202242]
36. Mentis MJ, McIntosh AR, Perrine K, et al. Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. *Am J Psychiatry*. 2002; 159:746–754. [PubMed: 11986127]
37. Huang C, Mattis P, Tang C, Perrine K, Carbon M, Eidelberg D. Metabolic brain networks associated with cognitive function in Parkinson's disease. *Neuroimage*. 2007; 34:714–723. [PubMed: 17113310]
38. Emre M, Aarsland D, Brown R, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. *Mov Disord*. 2007; 22:1689–1707. [PubMed: 17542011]
39. Dubois B, Burn D, Goetz C, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations for the Movement Disorder Society Task Force. *Mov Disord*. 2007; 16:2314–2324. [PubMed: 18098298]
40. Pagonabarraga J, Kulisevsky J, Llebaria G, García-Sánchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. *Mov Disord*. 2008; 23:998–1005. [PubMed: 18381647]
41. Kalbe E, Calabrese P, Kohn N, et al. Screening for cognitive deficits in Parkinson's disease with the Parkinson neuropsychometric dementia assessment (PANDA) instrument. *Parkinsonism Relat Disord*. 2008; 14:93–01. [PubMed: 17707678]
42. Marinus J, Visser M, Verwey A, et al. Assessment of cognition in Parkinson's disease. *Neurology*. 2003; 61:1222–1228. [PubMed: 14610124]
43. Hoops S, Nazem S, Siderowf AD, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson's disease. *Neurology*. 2009; 73:1738–1745. [PubMed: 19933974]
44. Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med*. 2004; 351:2509–2518. [PubMed: 15590953]
45. Aarsland D, Ballard C, Walker Z, et al. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol*. 2009; 8:613–618. [PubMed: 19520613]

46. Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomized, double-blind, placebo-controlled trial. *Lancet Neurol.* 2010; 9:969–977. [PubMed: 20729148]
47. Allain H, Schuck S, Manduit N. Depression in Parkinson's disease. *Br Med J.* 2000; 320:1287–1288. [PubMed: 10807601]
48. Tandberg E, Larsen JP, Aarsland D, et al. The occurrence of depression in Parkinson's disease. A community-based study. *Arch Neurol.* 1996; 53:175–179. [PubMed: 8639068]
49. Starkstein SE, Petracca G, Chemerinski E, et al. Depression in classic versus akinetic-rigid Parkinson's disease. *Mov Disord.* 1998; 13:29–33. [PubMed: 9452322]
50. Reijnders JSAM, Ehrh U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord.* 2008; 23:183–189. [PubMed: 17987654]
51. Starkstein SE, Preziosi TJ, Bolduc PL, et al. Depression in Parkinson's disease. *J Nerv Ment Dis.* 1990; 178:27–31. [PubMed: 2295885]
52. Leentjens AF, Lousberg R, Verhey FRJ. Markers for depression in Parkinson's disease. *Acta Psychiatr Scand.* 2002; 106:196–201. [PubMed: 12197857]
53. Cole SA, Woodard JL, Juncos JL, et al. Depression and disability in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 1996; 8:20–25. [PubMed: 8845697]
54. Lou J-S, Kearns G, Oken B, et al. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Mov Disord.* 2001; 16:190–196. [PubMed: 11295769]
55. Aarsland D, Larsen JP, Cummings JL, Laake K. Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. *Arch Neurol.* 1999; 56:595–601. [PubMed: 10328255]
56. Marsh L, Williams JR, Rocco M, Grill S, Munro C, Dawson TM. Psychiatric comorbidities in patients with Parkinson disease and psychosis. *Neurology.* 2004; 63:293–300. [PubMed: 15277623]
57. Caap-Ahlgren M, Dehlin O. Insomnia and depressive symptoms in patients with Parkinson's disease. Relationship to health-related quality of life. An interview of patients living at home. *Arch Gerontol Geriatr.* 2001; 32:23–33. [PubMed: 11251236]
58. Leentjens AF. Depression in Parkinson's disease: conceptual issues and clinical challenges. *J Geriatr Psychiatry Neurol.* 2004; 17:120–126. [PubMed: 15312275]
59. Leentjens AF, Marinus J, Van Hilten JJ, et al. The contribution of somatic symptoms to the diagnosis of depression in Parkinson's disease: a discriminant analytic approach. *J Neuropsychiatry Clin Neurosci.* 2003; 15:74–77. [PubMed: 12556575]
60. Stenager EN, Wermuth L, Stenager E, Boldsen J. Suicide in patients with Parkinson's disease: an epidemiological study. *Acta Psychiatr Scand.* 1994; 90:70–72. [PubMed: 7976453]
61. Nazem S, Siderowf AD, Duda JE, et al. Suicidal and death ideation in Parkinson's disease. *Mov Disord.* 2008; 10:1573–1579. [PubMed: 18618660]
62. Ehmann TS, Beninger RJ, Gawel MJ, Riopelle RJ. Depressive symptoms in Parkinson's disease: a comparison with disabled control subjects. *J Geriatr Psychiatry Neurol.* 1990; 3:3–9. [PubMed: 2140682]
63. Menza MA, Mark MH. Parkinson's disease and depression: the relationship to disability and personality. *J Neuropsychiatry Clin Neurosci.* 1994; 6:165–169. [PubMed: 8044039]
64. Tandberg E, Larsen JP, Aarsland D, Laake K, Cummings JL. Risk factors for depression in Parkinson disease. *Arch Neurol.* 1997; 54:625–630. [PubMed: 9152120]
65. Fang G, Xu Q, Park Y, et al. Depression and subsequent risk of Parkinson's disease in the NIH-AARP Diet and Health Study. *Mov Disord.* 2010; 25:1157–1162. [PubMed: 20310050]
66. Alonso A, Rodriguez LAG, Logroscino G, Hernan MA. Use of antidepressants and the risk of Parkinson's disease: a prospective study. *J Neurol Neurosurg Psychiatry.* 2009; 80:671–675. [PubMed: 19448091]
67. Feldmann A, Illes Z, Kosztolanyi P, et al. Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study. *Mov Disord.* 2008; 23:42–46. [PubMed: 17973326]

68. Cardoso EF, Maia FM, Fregni F, et al. Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. *Neuroimage*. 2009; 47:467–472. [PubMed: 19398020]
69. Walter U, Skoloudik D, Berg D. Transcranial sonography findings related to non-motor features of Parkinson's disease. *J Neurol Sci*. 2010; 289:123–127. [PubMed: 19735925]
70. Mayberg HS. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull*. 2003; 65:193–207. [PubMed: 12697626]
71. Murai T, Muller U, Werheid K, et al. In vivo evidence for differential association of striatal dopamine and midbrain serotonin systems with neuropsychiatric symptoms in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 2001; 13:222–228. [PubMed: 11449029]
72. Hesse S, Meyer PM, Strecker K, et al. Monoamine transporter availability in Parkinson's disease patients with or without depression. *Eur J Nucl Med Mol Imaging*. 2009; 36:428–435. [PubMed: 19037640]
73. Weintraub D, Newberg AB, Cary MS, et al. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. *J Nucl Med*. 2005; 46:227–232. [PubMed: 15695780]
74. Felicio AC, Moriyama TS, Godeiro-Junior C, et al. Higher dopamine transporter density in Parkinson's disease patients with depression. *Psychopharmacology (Berl)*. 2010; 211:27–31. [PubMed: 20495790]
75. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Mov Disord*. 2007; 22:1077–1092. [PubMed: 17394234]
76. Marsh L, McDonald WM, Cummings JL, et al. Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH work group. *Mov Disord*. 2006; 21:148–158. [PubMed: 16211591]
77. Althaus A, Becker OA, Spottke A, et al. Frequency and treatment of depressive symptoms in a Parkinson's disease registry. *Parkinsonism Relat Disord*. 2008; 14:626–632. [PubMed: 18406197]
78. Shulman LM, Taback RL, Rabinstein AA, et al. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*. 2002; 8:193–197. [PubMed: 12039431]
79. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. *J Geriatr Psychiatry Neurol*. 2003; 16:178–183. [PubMed: 12967062]
80. Richard IH, Kurlan R, Parkinson Study Group. A survey of antidepressant use in Parkinson's disease. *Neurology*. 1997; 49:1168–1170. [PubMed: 9339713]
81. 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; 23:850–857. [PubMed: 18311826]
82. Menza M, Dobkin RD, Marin H, et al. A controlled trial of anti-depressants in patients with Parkinson's disease and depression. *Neurology*. 2009; 72:886–892. [PubMed: 19092112]
83. Wermuth L, Sørensen PS, Timm S, et al. Depression in idiopathic Parkinson's disease treated with citalopram: a placebo-controlled trial. *Nord J Psychiatry*. 1998; 52:163–169.
84. Leentjens AF, Vreeling FW, Luijckx GJ, et al. SSRIs in the treatment of depression in Parkinson's disease. *Int J Geriatr Psychiatry*. 2003; 18:552–554. [PubMed: 12789682]
85. 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; 9:573–580. [PubMed: 20452823]
86. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson's disease. *Neurology*. 2010; 75:448–455. [PubMed: 20679638]
87. Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N. The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: a randomized, double-blind, placebo-controlled study. *Mov Disord*. 2010; 25:2311–2317. [PubMed: 20740485]

88. da Silva T, Munhoz R, Alvarez C, et al. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J Affect Disord.* 2008; 111:351–359. [PubMed: 18485485]
89. Dobkin RD, Allen LA, Menza M. Cognitive-behavioral therapy for depression in Parkinson's disease: a pilot study. *Mov Disord.* 2007; 22:946–952. [PubMed: 17377926]
90. Sproesser E, Viana MA, Quagliato EMAB, de Souza EAP. The effect of psychotherapy in patients with PD: a controlled study. *Parkinsonism Relat Disord.* 2010; 16:298–300. [PubMed: 19864172]
91. Oehlberg K, Barg FK, Weintraub D, et al. How depressed Parkinson's disease patients view the etiology and treatment of depression. *J Geriatr Psychiatry Neurol.* 2008; 21:123–132. [PubMed: 18474721]
92. Fénelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the prelevodopa era. *Neurology.* 2006; 66:93–98. [PubMed: 16401853]
93. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al. A 12-year population-based study of psychosis in Parkinson disease. *Arch Neurol.* 2010; 67:996–1001. [PubMed: 20697051]
94. Fenelon G, Soulas T, Zenasni F, de Langavant LC. The changing face of Parkinson's disease-associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. *Mov Disord.* 2010; 25:763–766. [PubMed: 20437542]
95. Arnulf I, Bonnet AM, Damier P, et al. Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology.* 2000; 55:281–288. [PubMed: 10908906]
96. Pacchetti C, Manni R, Zangaglia R, et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. *Mov Disord.* 2005; 20:1439–1448. [PubMed: 16028215]
97. Henderson MJ, Mellers JDC. Psychosis in Parkinson's disease: 'between a rock and a hard place'. *Int Rev Psychiatry.* 2000; 12:319–334.
98. Sanchez-Ramos JR, Ortoll R, Paulson GW. Visual hallucinations associated with Parkinson disease. *Arch Neurol.* 1996; 53:1265–1268. [PubMed: 8970453]
99. Wolters, ECh. Dopaminomimetic psychosis in Parkinson's disease patients: diagnosis and treatment. *Neurology.* 1999; 52(Suppl 3):S10–S13. [PubMed: 10227604]
100. Wolters, ECh. Intrinsic and extrinsic psychosis in Parkinson's disease. *J Neurol.* 2001; 248(Suppl 3):22–27.
101. Manganelli F, Vitale C, Santangelo G, et al. Functional involvement of central cholinergic circuits and visual hallucinations in Parkinson's disease. *Brain.* 2009; 132:2350–2355. [PubMed: 19584099]
102. Huot P, Johnston TH, Darr T, et al. Increased 5-HT<sub>2A</sub> receptors in the temporal cortex of Parkinsonian patients with visual hallucinations. *Mov Disord.* 2010; 25:1399–1408. [PubMed: 20629135]
103. Ballanger B, Strafella AP, Van Eimeren T, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol.* 2010; 67:416–421. [PubMed: 20385906]
104. Kurita A, Murakami M, Takagi S, Matsushima M, Suzuki M. Visual hallucinations and altered visual information processing in Parkinson disease and dementia with Lewy bodies. *Mov Disord.* 2010; 25:167–171. [PubMed: 20063433]
105. Ramirez-Ruiz B, Martí MJ, Tolosa E, et al. *Brain* response to complex visual stimuli in Parkinson's patients with hallucinations: a functional magnetic resonance imaging study. *Mov Disord.* 2008; 23:2335–2343. [PubMed: 18785653]
106. Boecker H, Ceballos-Baumann AO, Volk D, Conrad B, Forstl H, Haussermann P. Metabolic alterations in patients with Parkinson disease and visual hallucinations. *Arch Neurol.* 2007; 64:984–988. [PubMed: 17620488]
107. Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, et al. Frontal and associative visual areas related to visual hallucinations in dementia with Lewy bodies and Parkinson's disease with dementia. *Mov Disord.* 2010; 25:615–622. [PubMed: 20175186]
108. Ibarretxe-Bilbao N, Ramirez-Ruiz B, Junque C, et al. Differential progression of brain atrophy in Parkinson's disease with and without visual hallucinations. *J Neurol Neurosurg Psychiatry.* 2010; 81:650–657. [PubMed: 19965847]

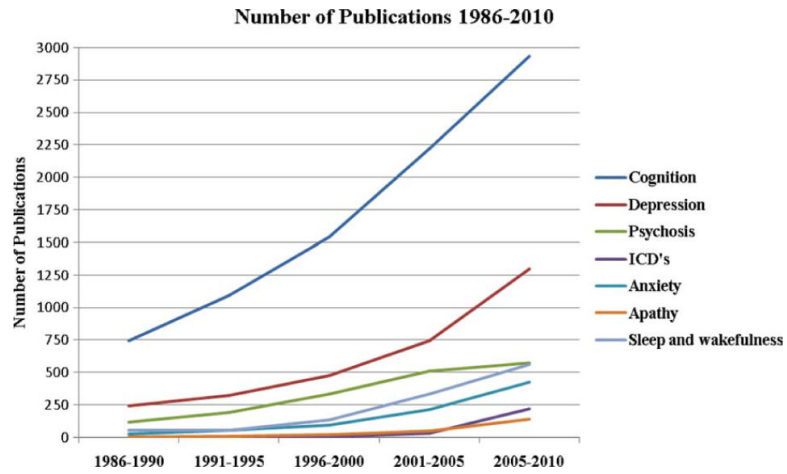
109. Fernandez HH, Aarsland D, Fénelon G, et al. Scales to assess psychosis in Parkinson's disease: critique and recommendations. *Mov Disord.* 2008; 23:484–500. [PubMed: 18175343]
110. Thomsen TR, Panisset M, Suchowersky O, Goodridge A, Mendis T, Lang AE. Impact of standard of care for psychosis in Parkinson disease. *J Neurol Neurosurg Psychiatry.* 2008; 79:1413–1415. [PubMed: 19010958]
111. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology.* 2001; 56(Suppl 5):S1–S88. [PubMed: 11402154]
112. 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; 20:958–963. [PubMed: 15800937]
113. Rabey JM, Prokhorov T, Miniowitz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labeled study of 3 months' duration. *Mov Disord.* 2007; 22:313–318. [PubMed: 17034006]
114. Shotbolt P, Samuel M, Fox C, David AS. A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. *Neuropsychiatr Dis Treat.* 2009; 5:327–332. [PubMed: 19557142]
115. The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med.* 1999; 340:757–763. [PubMed: 10072410]
116. The French Clozapine Parkinson Study Group. Clozapine in drug-induced psychosis in Parkinson's disease. *Lancet.* 1999; 353:2041–2042. [PubMed: 10376627]
117. Meltzer HY, Mills R, Revell S, et al. Pimavanserin, a serotonin<sub>2A</sub> receptor inverse agonist, for the treatment of Parkinson's disease psychosis. *Neuropsychopharmacology.* 2010; 35:881–892. [PubMed: 19907417]
118. Voon V, Fox SH. Medication-related impulse control and repetitive behaviors in Parkinson disease. *Arch Neurol.* 2007; 64:1089–1096. [PubMed: 17698698]
119. Weintraub D, Siderowf AD, Potenza MN, et al. Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol.* 2006; 63:969–973. [PubMed: 16831966]
120. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: A cross-sectional study of 3090 patients. *Arch Neurol.* 2010; 67:589–595. [PubMed: 20457959]
121. Weintraub D, Sohr M, Potenza MN, et al. Amantadine use associated with impulse control disorders in Parkinson disease in cross-sectional study. *Ann Neurol.* 2010; 68:963–968. [PubMed: 21154480]
122. Giovannoni G, O'sullivan JD, Turner K, Manson AJ, Lees AJL. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry.* 2000; 68:423–428. [PubMed: 10727476]
123. Evans AH, Katzenschlager R, Paviour D, et al. Punding in Parkinson's disease: its relation to the dopamine dysregulation syndrome. *Mov Disord.* 2004; 19:397–405. [PubMed: 15077237]
124. Miyasaki J, Hassan KL, Lang AE, Voon V. Punding prevalence in Parkinson's disease. *Mov Disord.* 2007; 22:1179–1181. [PubMed: 17230464]
125. Voon V, Reynolds B, Brezing C, et al. Impulsive choice and response in dopamine agonist-related impulse control behaviors. *Psychopharmacology (Berl).* 2010; 207:645–659. [PubMed: 19838863]
126. Housden CR, O'sullivan SS, Joyce EM, Lees AJ, Roiser JP. Intact reward learning but elevated delay discounting in Parkinson's disease patients with impulsive-compulsive spectrum behaviors. *Neuropsychopharmacology.* 2010; 35:2155–2164. [PubMed: 20631686]
127. Santangelo G, Vitale C, Trojano L, Verde F, Grossi D, Barone P. Cognitive dysfunctions and pathological gambling in patients with Parkinson's disease. *Mov Disord.* 2009; 24:899–905. [PubMed: 19205072]
128. Evans AH, Pavese N, Lawrence AD, et al. Compulsive drug use linked to sensitized ventral striatal dopamine transmission. *Ann Neurol.* 2006; 59:852–858. [PubMed: 16557571]

129. Steeves TDL, Miyasaki J, Zurowski M, et al. Increased striatal dopamine release in parkinsonian patients with pathological gambling: a  $^{11}\text{C}$  raclopride PET study. *Brain*. 2009; 132:1376–1385. [PubMed: 19346328]
130. Cilia R, Ko JH, Cho SS, et al. Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiol Dis*. 2010; 39:98–104. [PubMed: 20338240]
131. Voon V, Pessiglione M, Brezing C, et al. Mechanisms underlying dopamine-mediated reward bias in compulsive behaviors. *Neuron*. 2010; 65:135–142. [PubMed: 20152119]
132. Rao H, Mamikonyan E, Detre JA, et al. Decreased ventral striatal activity with impulse control disorders in Parkinson's disease. *Mov Disord*. 2010; 25:1660–1669. [PubMed: 20589879]
133. Mamikonyan E, Siderowf AD, Duda JE, et al. Long-term follow-up of impulse control disorders in Parkinson's disease. *Mov Disord*. 2008; 23:75–80. [PubMed: 17960796]
134. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol*. 2010; 67:58–63. [PubMed: 20065130]
135. Ardouin C, Voon V, Worbe Y, et al. Pathological gambling in Parkinson's disease improves on chronic subthalamic nucleus stimulation. *Mov Disord*. 2006; 21:1941–1946. [PubMed: 16972268]
136. Smeding HMM, Goudriaan AE, Foncke EMJ, Schuurman PR, Speelman JD, Schmand B. Pathological gambling after bilateral subthalamic nucleus stimulation in Parkinson disease. *J Neurol Neurosurg Psychiatry*. 2007; 78:517–519. [PubMed: 17210626]
137. Thomas A, Bonnani L, Gambi F, Di Iorio A, Onofrij M. Pathological gambling in Parkinson disease is reduced by amantadine. *Ann Neurol*. 2010; 68:400–404. [PubMed: 20687121]
138. Stacy M. Sleep disorders in Parkinson's disease: epidemiology and management. *Drugs Aging*. 2002; 19:733–739. [PubMed: 12390050]
139. Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclassification of nonmotor symptoms of Parkinson's disease to health care professionals: An international study using the Nonmotor Symptoms Questionnaire. *Mov Disord*. 2010; 25:6967–701.
140. Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. *Neurology*. 2010; 75:494–499. [PubMed: 20668263]
141. Jellinger K. The pedunculopontine nucleus in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1988; 51:540–543. [PubMed: 3379428]
142. Eisensehr I, Linke R, Noachtar S, et al. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behavior disorder. comparison with Parkinson's disease and controls. *Brain*. 2000; 123:1155–1160. [PubMed: 10825354]
143. Phillips B. Movement disorders: a sleep specialist's perspective. *Neurology*. 2004; 62(Suppl 2):S9–S16. [PubMed: 15007159]
144. Tandberg E, Larsen JP, Karlsen K. Excessive daytime sleepiness and sleep benefit in Parkinson's disease: a community-based study. *Mov Disord*. 1999; 14:922–927. [PubMed: 10584665]
145. Schifitto G, Friedman JH, Oakes D, et al. Fatigue in levodopa-naive subjects with Parkinson disease. *Neurology*. 2008; 71:481–485. [PubMed: 18695158]
146. Karlsen K, Larsen JP, Tandberg E, et al. Fatigue in patients with Parkinson's disease. *Mov Disord*. 1999; 14:237–241. [PubMed: 10091615]
147. Hobson DE, Lang AE, Martin WR, Razmy A, Rivest J, Fleming J. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: a survey by the Canadian Movement Disorders Group. *JAMA*. 2005; 287:455–463. [PubMed: 11798367]
148. Dowling GA, Mastick J, Colling E, Carter JH, Singer CM, Aminoff MJ. Melatonin for sleep disturbances in Parkinson's disease. *Sleep Med*. 2005; 6:459–466. [PubMed: 16084125]
149. Medeiros CAM, de Bruin PFC, Lopes LA, Magalhaes MC, Seabra MDL, de Bruin VMS. Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson's disease: a randomized, double blind, placebo-controlled study. *J Neurol*. 2007; 254:459–464. [PubMed: 17404779]
150. Menza M, Dobkin RD, Marin H, et al. Treatment of insomnia in Parkinson's disease: a controlled trial of eszopiclone and placebo. *Mov Disord*. 2010; 25:1708–1714. [PubMed: 20589875]

151. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry*. 2005; 76:1636–1639. [PubMed: 16291885]
152. Adler CH, Caviness JN, Hentz JG, et al. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord*. 2003; 18:287–293. [PubMed: 12621632]
153. Hogl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep*. 2002; 25:62–66.
154. Lou J-S, Dimitrova DM, Park BS, et al. Using modafinil to treat fatigue in Parkinson disease: a double-blind, placebo-controlled pilot study. *Clin Neuropharmacol*. 2009; 32:305–310. [PubMed: 19620846]
155. Mendonça DA, Menezes K, Jog MS. Methylphenidate improves fatigue scores in Parkinson disease: a randomized controlled trial. *Mov Disord*. 2007; 22:2070–2076. [PubMed: 17674415]
156. Voon V, Kubu C, Krack P, Houeto JL, Tröster AI. Deep brain stimulation: neuropsychological and neuropsychiatric issues. *Mov Disord*. 2006; 21(Suppl. 14):S305–S326. [PubMed: 16810676]
157. Appleby BS, Duggan PS, Reagenberg A, Rabins PV. Psychiatric and neuropsychiatric adverse events associated with deep brain stimulation: a meta-analysis of ten years' experience. *Mov Disord*. 2007; 22:1722–1728. [PubMed: 17721929]
158. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurol*. 2006; 5:578–588. [PubMed: 16781988]
159. 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; 7:605–614. [PubMed: 18538636]
160. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized clinical trial. *JAMA*. 2009; 301:63–73. [PubMed: 19126811]
161. Frankemolle AMM, Wu J, Noecker AM, et al. Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. *Brain*. 2010; 133:746–761. [PubMed: 20061324]
162. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006; 355:896–908. [PubMed: 16943402]
163. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2010; 362:2077–2091. [PubMed: 20519680]
164. Voon V, Krack P, Lang AE, et al. A multicentre study on suicide outcomes following subthalamic stimulation for Parkinson's disease. *Brain*. 2008; 131:2720–2728. [PubMed: 18941146]
165. Witjas T, Kaphan E, Azulay JP, et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology*. 2002; 59:408–413. [PubMed: 12177375]
166. Richard IH, Justus AW, Kurlan R. Relationship between mood and motor fluctuations in Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 2001; 13:35–41. [PubMed: 11207327]
167. Kulisevsky J, Pascual-Sedano B, Barbanoj M, Gironell A, Pagonabarraga J, García-Sánchez C. Acute effects of immediate and controlled-release levodopa on mood in Parkinson's disease: a double-blind study. *Mov Disord*. 2007; 22:62–67. [PubMed: 17115388]
168. Maricle RA, Nutt JG, Carter JH. Mood and anxiety fluctuation in Parkinson's disease associated with levodopa infusion: preliminary findings. *Mov Disord*. 1995; 10:329–332. [PubMed: 7651451]
169. Richard IH, Schiffer RB, Kurlan R. Anxiety and Parkinson's disease. *J Neuropsychiatry Clin Neurosci*. 1996; 8:383–92. [PubMed: 9116473]
170. Kummer A, Cardoso F, Teixeira AL. Frequency of social phobia and psychometric properties of the Liebowitz social anxiety scale in Parkinson's disease. *Mov Disord*. 2008; 23:1739–1743. [PubMed: 18661550]



171. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. *Mov Disord.* 2009; 24:1333–1338. [PubMed: 19425086]
172. Dissanayaka NNW, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov Disord.* 2010; 25:838–845. [PubMed: 20461800]
173. Gonera EG, van't Hof M, Berger HJC, et al. Symptoms and duration of the prodromal phase in Parkinson's disease. *Mov Disord.* 1997; 12:871–876. [PubMed: 9399209]
174. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's Disease: a case-control study. *Mov Disord.* 2000; 15:669–677. [PubMed: 10928577]
175. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 1992; 4:134–139. [PubMed: 1627973]
176. Starkstein SE, Merello M, Jorge R, Brockman S, Bruce D, Power B. The syndromic validity and nosological position of apathy in Parkinson's disease. *Mov Disord.* 2009; 24:1211–1216. [PubMed: 19412942]
177. Kirsch-Darrow L, Fernandez HF, Marsiske M, Okun MS, Bowers D. Dissociating apathy and depression in Parkinson disease. *Neurology.* 2006; 67:33–38. [PubMed: 16832074]
178. Isella V, Melzi P, Grimaldi M, et al. Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Mov Disord.* 2002; 17:366–371. [PubMed: 11921125]
179. Reijnders JSAM, Scholtissen B, Weber WEJ, Aalten P, Verhety FRJ, Leentjens AFG. Neuroanatomical correlates of apathy in Parkinson's disease: a magnetic resonance imaging study using voxel-based morphometry. *Mov Disord.* 2010; 25:2318–2325. [PubMed: 20669264]
180. Thobois S, Ardouin C, Lhommée E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain.* 2010; 133:1111–1127. [PubMed: 20237128]
181. Mavandadi S, Nazem S, Ten Have TR, et al. Use of latent variable modeling to delineate psychiatric and cognitive profiles in Parkinson's disease. *Am J Geriatr Psychiatry.* 2009; 17:986–995. [PubMed: 19855199]
182. van Rooden SM, Visser M, Verbaan D, Marinus J, Van Hilten JJ. Patterns of motor and non-motor features in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2009; 80:846–850. [PubMed: 19211596]
183. Chaudhuri KR, Martinez-Martin P, Brown RG, et al. The metric properties of a novel non-motor symptoms scale for Parkinson's disease: results from an international pilot study. *Mov Disord.* 2007; 22:1901–1911. [PubMed: 17674410]
184. Visser M, Verbaan D, van Rooden SM, Stiggelbout AM, Marinus J, Van Hilten JJ. Assessment of psychiatric complications in Parkinson's disease: the SCOPA-PC. *Mov Disord.* 2007; 22:2221–2228. [PubMed: 17712843]
185. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology.* 1994; 44:2308–2314. [PubMed: 7991117]
186. Ponce FA, Lozaone AM. The most cited works in Parkinson's disease. *Mov Disord.* Nov 10.2010 [Epub ahead of print]. DOI: 10.1002/mds.23445.



**FIG. 1.** Number of articles published devoted to Parkinson's disease, 1986–2010. *Cognition* = Parkinson\* and (dementia or cognitive impairment); *Depression* = Parkinson\* and depression; *Psychosis* = Parkinson\* and (psychosis or hallucination); *Anxiety* = Parkinson\* and anxiety; *ICD's* = Parkinson\* and (impulse control disorder or dopamine dysregulation syndrome); *Sleep and wakefulness* = Parkinson\* and (insomnia or sleepiness or fatigue or REM); *Apathy* = Parkinson\* and apathy.