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

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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

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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.[1]

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[2–6]; (2) dementia (PDD) is a common long-term outcome, affecting up to 80% of patients[7]; (3) approximately 25% of nondemented (PD-ND) patients have mild cognitive impairment (PD-MCI),[5] with PD-MCI patients at increased risk of developing PDD[8]; and (4) a significant percentage of newly diagnosed PD patients have cognitive deficits[9,10] and experience cognitive decline over a several-year period.[11] 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).[12–18] 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[19–21]; (2) in addition, a significant percentage of PD patients also have AD-related neuropathological changes at autopsy,[22] and AD CSF biomarkers are associated with cognitive impairment and decline in PD[23]; (3) a range of neurotransmitter deficits are associated with cognitive impairment, including acetylcholine,[24] dopamine,[25–27] and norepinephrine[28]; (4) impairments in the corticostriatal neural circuitry likely contribute to cognitive impairment in PD[29]; (5) a range of genetic influences for specific cognitive impairments or decline have been identified, including brain-derived neurotrophic factor val^{66}met,[30] catechol-O-methyl-transfer-ase val^{158}met,[31] and microtubule-associated protein tau polymorphisms[17]; and (6) diffuse (primarily medial temporal lobe, parietal lobe, and prefrontal cortex) gray and white matter neurodegeneration[32–35] and metabolic deficits are associated with cognitive decline.[36,37] 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[38] and published an algorithm for diagnosing PDD.[39] 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,[40] the Parkinson Neuropsychometric Dementia Assessment,[41] the Scales for Outcomes of Parkinson's Disease–Cognition,[42] the Dementia Rating Scale–2, and the Montreal Cognitive Assessment.[43]

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.[44] 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[45] but not the other.[46]

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.[47–50] Another advance is our understanding of numerous correlates or possible risk factors for dPD, including female sex,[48] a personal[51] or family[52] history of depression, early-onset PD,[53] “atypical” parkinsonism,[49] and psychiatric comorbidity (eg, worse cognition, psychosis, anxiety, apathy, fatigue, and insomnia[48,54–57]). 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.[58] Not surprisingly, core non-somatic symptoms of depression discriminate most highly between depressed and nondepressed (ie, less likelihood of symptom overlap).[59] It has almost become dogma that suicide is uncommon in PD,[60] yet recent research challenges this and suggests that both death and suicidal ideation may be relatively common.[61]

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,[62] that there is an association between severity of depression and PD,[63,64] and that depression may be a prodromal syndrome in some PD patients.[65,66] 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.[36,67–74]

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

Up to 25% of PD patients are now on an antidepressant at any given time, most commonly a selective serotonin reuptake inhibitor (SSRI),[79,80] 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,[81,82] but only 1 of 3 controlled SSRI studies reporting positive findings, although sample sizes were small.[81,83,84] 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[85]; (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[86]; (3) left PFC repetitive transcranial magnetic stimulation (rTMS), which was efficacious[87]; and (4) omega-3 fatty acid (ie, fish oil), which was efficacious.[88] Finally, psychotherapy is increasingly being explored as a treatment of dPD,[89,90] 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.[91] 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,[92] a recent prospective study that encompassed currently available treatments reported a long-term cumulative prevalence of 60%.[93] Visual hallucinations are most commonly reported in PD, but auditory, tactile, and olfactory hallucinations are also relatively common.[94] The overwhelming majority of PD-P patients also report disturbances of sleep and wakefulness, including REM behavior disorder (RBD)[95,96]; other correlates or risk factors are exposure to PD medications,[97] older age,[55] and greater cognitive impairment.[56]

Despite the association between medication exposure and PD-P, the dosage and duration of antiparkinsonian treatment do not clearly correlate with psychosis,[55,98] 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_2/D_3 receptors[99]. Cholinergic deficits and a serotonergic/dopaminergic imbalance using a range of imaging modalities and other neural probes have also been implicated,[99–101] particularly in the primary visual system and dorsal/ventral visual association pathways.[102–106] Finally, neurodegeneration of widespread limbic, paralimbic, and neocortical gray matter, including the PFC, is associated with PD-P.[107,108]

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,[109] 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.[110] 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.[111] 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.[112–114] Two notable randomized clinical trials showed that clozapine is efficacious for PD-P,[115,116] yet the drug is rarely used because of the requirement for routine blood monitoring. A recent controlled study of pimavanserin, a serotonin$_{2A}$ receptor inverse agonist with a promising receptor binding profile, was negative,[117] 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.[118] 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.[119]

In a recent large multisite observational study, an ICD was identified in 14% of PD patients, and 4% had comorbid ICDs.[120] ICDs were more common in patients taking a DA. Both levodopa[120] and amantadine[121] 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[118] 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.[122] Punding (ie, repetitive, non-goal-directed activity) was reported in 14% of PD patients on higher levodopa dosages in 1 study,[123] but another larger study of unselected PD patients reported a frequency < 2%.[124]

A range of cognitive impairments have been reported in PD ICD patients, most commonly executive deficits, including impulsive decision-making.[125–127] The dopamine system has been implicated, with both ICD and DDS patients having sensitized D_2/D_3 receptors,[128,129] and decreased dopamine transporter availability in ICD patients.[130] Functional imaging studies have reported altered striatal activation and corticostriatal connectivity in ICD patients.[131,132]

ICD behaviors often resolve after discontinuing DA treatment.[133] However, many patients do not want or tolerate DA discontinuation, and a DA withdrawal syndrome (DAWS) was recently described.[134] The relationship between deep brain stimulation (DBS) and ICDs is complex. Subthalamic nucleus (STN) DBS has been associated with improvement in ICD symptoms,[135] but there is also anecdotal evidence that ICDs may begin or worsen transiently post-DBS surgery.[136] 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.[137]

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.[138,139] RBD, along with impaired olfaction and depression/anxiety, may be a key clinical feature of the important nonmotor prodrome of PD.[140] 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.[138] RBD and other sleep disturbances have been attributed both to progressive degeneration of the cholinergic pedunculopontine nucleus (PPN)[141] and reduced striatal dopaminergic activity.[142] Associated clinical factors that can disrupt sleep in PD patients are parkinsonism, autonomic symptoms, and psychiatric/cognitive disorders.[12,138,143]

Excessive daytime sleepiness (EDS) and fatigue (physical or mental) are common in PD,[144,145] 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.[138,143] As with RBD, psychiatric comorbidity[144,146] 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.[147]

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,[148,149] and a controlled trial of eszopiclone (a nonbenzodiazepine hypnotic) was partially positive.[150] Evidence has been mixed for modafinil[151–154] and psychostimulants[155] 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.[156,157] A recent meta-analysis[158] and 2 controlled studies of DBS versus best medical therapy (BMT)[159,160] 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,[161] 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.[156] In controlled DBS studies, there were no between-group differences in mood post-DBS surgery,[160,162] and 1 study reported improvement in anxiety symptoms with DBS.[159] 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.[163] Clinically, pre- and post-DBS psychiatric and cognitive monitoring are important, especially given reports of postsurgical suicide ideation and completed or attempted suicide.[164]

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.[165] The relationship between motor status and NMFs is complex, as there is not always a correlation between affect and motor state,[166,167] and improvements in mood post- levodopa infusion in patients with MFs can precede improvements in motor status.[168] 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.[169–172] Increasing anxiety and discrete anxiety attacks have been associated with NMFs, particularly the onset of "off" periods.[171,172] Similar to depression, there is an increased frequency of anxiety disorders up to 20 years prior to PD onset,[173,174] 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[175,176] and can occur independently of depression and cognitive impairment, although overlap is common.[175,177] Studies of apathy in PD have reported associations with executive deficits, verbal memory impairment, and bradyphrenia,[175,178] with decreased cingulate and inferior frontal gyri volumes.[179] 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.[180]

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.[181] In another study using factor analysis, the first and strongest of 4 factors included cognitive impairment, psychotic symptoms, depression, and EDS.[182]

Recently, several global assessment instruments have been developed and tested for clinical use in PD, including the Non-Motor Symptoms Scale[183] and the Scales for Outcomes in Parkinson's Disease–Psychiatric Complications.[184] In addition, the Neuropsychiatric Inventory[185] 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.[186] 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.

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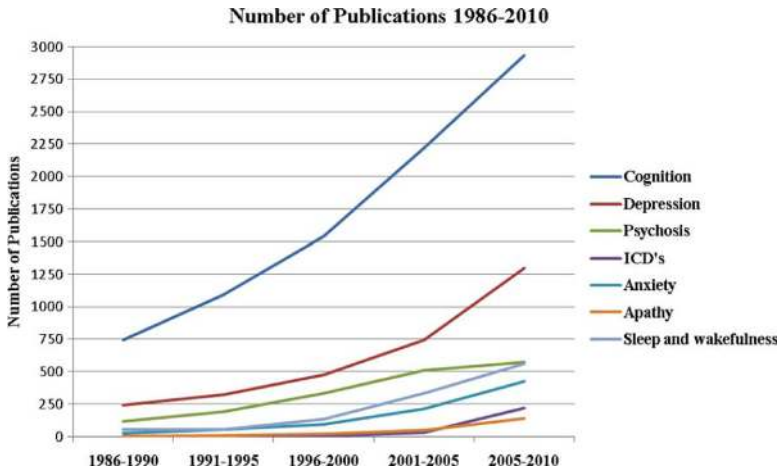

FIG. 1.

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.