American Journal of Alzheimer's Disease & Other Dementias®
2016, Vol. 31(7) 585-594

DOI: 10.1177/1533317516653823
aja.sagepub.com
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Clinical Epidemiology, Evaluation, and Management of Dementia in Parkinson Disease

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Abstract

The prevalence of neurodegenerative diseases such as Parkinson disease (PD) will increase substantially, due to the aging of the population and improved treatments leading to better disease-related outcomes. Dementia is the most common nonmotor symptom in PD, and most patients with PD will have cognitive dysfunction and cognitive decline in the course of their disease. The development of cognitive dysfunction in PD greatly limits the ability to participate in activities of daily living and can be a tipping point for nursing home placement or major caregiver stress. Understanding the different causes of dementia and how to reduce the incidence and impact of secondary cognitive dysfunction in PD are necessary skills for primary care physicians and neurologists. In this review, we discuss the clinical epidemiology of dementia in PD with an emphasis on preventable cognitive dysfunction, present tools for outpatient evaluation of cognitive dysfunction, and describe current pharmacological treatments for dementia in PD.

Keywords

Parkinson disease, dementia, mild cognitive impairment, Parkinson disease with dementia, epidemiology

Introduction

Once thought to be a distinct motor disorder characterized by bradykinesia, rigidity, rest tremor and postural instability,[1] Parkinson disease (PD) is now recognized to be a heterogeneous neurodegenerative syndrome with motor and nonmotor symptoms. Common nonmotor symptoms in PD relate to impaired autonomic (orthostasis, urinary frequency/urgency, slowed intestinal transit), psychiatric (depression, anxiety, impulse control disorders, psychosis, apathy), and psychosocial (punding, apathy) functions. The most common nonmotor feature of PD, however, is cognitive dysfunction. In this article, we provide a review of the current literature on the epidemiology of cognitive impairment in PD, decomposing what is the current body of knowledge into modifiable and fixed risk factors. We also discuss rational approaches to the diagnosis and treatment of dementia in PD.

Epidemiology of Cognitive Impairment in PD

Both cross-sectional and longitudinal studies suggest that cognitive impairment is the most common nonmotor feature of PD. Although the point prevalence of dementia in PD is reported between 25% and 30%,[2,3] longitudinal data support the theory that dementia is an inevitable manifestation of the disease. A clinic-based study of 224 individuals with PD in Norway demonstrated that 19% of newly diagnosed cases of PD had measurable cognitive impairment at disease presentation.[4] Over the next 8 years, more than three-fourth of this cohort with PD developed frank dementia (prevalence = 78.2%, 95% CI 71.1%-84.0%). Similarly, an administrative data study of over 138 000 US Medicare beneficiaries with an incident PD diagnosis found 69.6% of new PD cases were diagnosed with dementia within 6 years.[5] Finally, a multicenter longitudinal study of 136 incident patients with PD in the Sydney multicenter study of PD found that dementia was present in 83% of 20-year survivors, regardless of the age at disease onset.[6,7] Data from an ongoing longitudinal study of patients with PD with normal cognition at study entry highlight the rapid decline in function clinicians often observe; 47% of study patients

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developed mild cognitive impairment (MCI) within 6 years, and 100% of these new cases of MCI transitioned to frank PDD within 5 years of MCI diagnosis.[8]

Cumulative prevalence data suggest that clinically apparent cognitive dysfunction, ranging from MCI to severe dementia develops nearly universally in patients with PD. However, the underlying pathophysiology of dementia in PD can vary significantly, and these variations can be seen at the cellular, patient, and population levels. A comprehensive discussion of the neuropathology of dementia in PD is beyond the scope of this review, but a recent clinicopathological study of patients with PD with dementia compares two major pathological subgroups: prominent neocortical synucleinopathy (Lewy bodies) and neocortical synucleinopathy plus Alzheimer pathological changes (β-amyloid deposited as Aβ plaques or tau protein forming neurofibrillary tangles).[9-11] These two pathological subgroups could not be distinguished based on patient characteristics or clinical assessments by movement disorders specialists, but individuals with mixed pathology had a shorter survival after dementia diagnosis. Although future studies are needed to understand how Aβ accumulation is linked to pathological synucleinopathy in PD, current data suggest that the neuropathology of "classic" PD dementia (commonly referred to as PDD) is mixed.[12,13]

Having postural instability and gait dysfunction (falls, freezing) as presenting motor features of PD are the most widely recognized clinical predictors of both suboptimal anti-Parkinson medication response and early cognitive dysfunction in PD.[14-16]

A 7-year longitudinal study in India assessed the risk factors for the development of dementia in PD.[17] In this cohort, early hallucinations (odds ratio [OR] = 4.42), akinetic/tremor dominant form of PD (OR = 0.380), and asymmetrical disease onset (OR = 0.3285) were associated with increased odds of dementia. Patients with PDD showed more functional decline, were in a higher Hoehn and Yahr (the most commonly used clinical staging system for PD) stage of the disease, and had PD for a longer duration. Recently, a university-based cohort study of 80 individuals with PD without dementia at baseline identified several other clinical predictors of dementia. In this cohort, the presence of MCI (OR = 22.5), REM sleep behavior disorder (OR = 49.7), hypertension (OR = 1.37 per 10 mm Hg), or orthostasis (OR = 1.84 per 10 mm Hg drop) at baseline predicted the development of dementia over 4 years.[18] Hypertension is not a feature of PD, yet, effective management of hypertension may be affected by having PD. As we continue to discuss below, clinical epidemiology data such as these support a multifactorial approach to the delay and prevention of cognitive impairment in PD.

Parkinson disease is most common among white men, and most PD research in the United States focuses on academic center populations.[19] There is limited data describing PD clinical features and disease course in individuals who are women, not white, because these groups are underrepresented in tertiary movement disorders clinics. Recent studies using Medicare (a US government sponsored insurance program that is utilized by 98% of Americans older than 65 years) claims data suggest that there are demographic differences in the diagnosis of dementia in PD. In a cohort study of >138 000 incident PD cases followed 6 years, 78.2% of black and 73.1% of hispanic patients with PD were diagnosed with dementia within 6 years (compared to 69.6% in the overall PD population). Regression models that included reported ethnicity/ancestry, age, and sex found the odds of dementia were greater in blacks and hispanics (vs whites adjusted OR [AOR] = 1.72, 1.63-1.81 and AOR = 1.26, 1.16-1.37, respectively).[5] Asian Americans had lower adjusted odds of dementia (AOR = 0.89, 0.79-0.99). Women with PD were more likely than men to be diagnosed with dementia (AOR = 1.13, 1.11-1.16), after adjusting for age and ancestry/ethnicity. Interestingly, these differences are similar to the ancestry/ethnicity and gender patterns seen in Alzheimer disease[20,21] and may in part reflect the increased prevalence of Alzheimer dementia in women and blacks.[5,22] These data may also indicate that there is unique pattern of PD progression among minorities and women with PD or represent disparities in quality care for comorbid disease, including poorly controlled blood pressure and diabetes (conditions which predispose to vascular dementia).[23] A portion of the demographic differences in observed PDD may be explained by greater educational achievement by white males; a weak inverse relationship between level of education and cognitive decline has been demonstrated by many studies.[24] Future clinicopathological studies of groups at higher or lower risk of dementia may improve the understanding of these phenomena.

Genetic Risk Factors for Dementia in PD

Genetic risk factors for cognitive decline in PD that have been identified thus far include microtubule-associated protein tau (MAPT), glucocerebrosidase (GBA), apolipoprotein E (APOE), mitochondrial transcription factor A (TFAM), and brain-derived neurotrophic factor (BDNF). A 10-year prospective cohort study found MAPT H1/H1 genotype was associated with increased rate of cognitive decline and development of early dementia.[25] Another prospective study found that patients with GBA mutation were 5.8 times more likely to have a clinical diagnosis of MCI or dementia combined (95% CI 1.7-19.9, $P = .005$).[26] The APOE genotype is a known factor in susceptibility to AD and several studies examined the risk of clinical PDD and APOE status. Meta-analysis data demonstrate patients with ε4 allele of APOE were more likely to have clinical PDD (OR: 1.6, 95% CI 0.18-1.6), possibly indicating concurrent AD or other APOE-associated dementia or highlighting the diversity of pathophysiological mechanisms underlying a clinical PDD diagnosis.[27,28] The BDNF has an important role in the frontostriatal circuitry by interacting with dopaminergic transmission and dopamine receptor stimulation. In a case–control study, comparing 294 patients with PD and 233 age- and sex-matched healthy controls, BDNF(AA) genotype was associated with near 6-fold increase in risk of cognitive impairment (OR: 5.7, 95% CI 1.9-16.6).[29] Gene-specific treatment currently do not exist, but current cross-discipline genetic and clinical epidemiology projects, such as the

Longitudinal Clinical and Genetic Studies of Parkinson's Disease and Parkinson's Progression Markers Initiative, seek to produce data that will lead to personalized clinical approaches and therapies for PDD.

Clinical Classification of Dementia Syndromes in PD

In spite of the clinical, pathological, and patient level-heterogeneity of dementia syndromes in PD presented above, the approach to classifying dementia in PD is fairly straightforward. The commonly used clinical term for chronic progressive cognitive impairment in individuals with PD remains PDD, in spite of the recent understanding that this label likely describes multiple pathological subgroups. Secondary causes of cognitive dysfunction in patients with PD can be thought of as *preventable* or *reversible*. Reversible dementia syndromes include dopaminergic medication intoxication/withdrawal, anticholinergic medication intoxication, other central nervous system (CNS) acting medication intoxication, depression, B12 deficiency, thyroid disorders. Preventable (but likely not reversible) dementia and cognitive dysfunction can occur due to chronic vascular, renal, liver disease.

Primary/neurodegenerative cognitive dysfunction in PD. The PDD is characterized by α synuclein aggregation in the subcortex, hence its early classification as a subcortical dementia. Current guidelines support a diagnosis of PDD when a person has clinical parkinsonism that fulfills criteria for PD (= 2 or more motor signs plus levodopa responsiveness and absence of atypical signs/symptoms[1]) at least 1 year before the appearance of cognitive impairment. Based on MDS criteria, the diagnosis of PDD is probable when there is impairment in 2 or more of the following cognitive domains: attention, executive function, visuospatial function, and memory.[30]

When cognitive dysfunction presents at or less than 1 year after motor symptoms, alternative diagnoses such as diffuse Lewy body disease (or another atypical neurodegenerative disease of the basal ganglia) should be considered. In clinical practice, the appearance of advanced dementia even 5 years after motor symptom onset should raise suspicion of an alternative/additional neurodegenerative disease or secondary cause(s) of cognitive dysfunction. Complicating the diagnosis of primary neurodegenerative dementia in Parkinson syndromes is the fact that there can be overlap in clinical presentation. For example, visuospatial dysfunction and fluctuations in attention can be seen in established PDD as well as Dementia with Lewy Bodies (DLB).[31] Neuropsychiatric symptoms, despite not being part of criteria for diagnosis of PDD, are oftentimes present. In 1 study of 537 patients with PDD, 64% had at least 1 neuropsychiatric symptom (depression, 58%; apathy, 54%; anxiety, 49%; and hallucinations, 44%; were the most common symptoms).[32,33]

Alzheimer dementia is the most common neurodegenerative disease affecting older adults, and having PD does not protect against developing AD. The core clinical criteria for AD require deficits in memory, language, visuospatial, and executive function.[34] In theory, the development of AD in a person with PD may be distinguished from PDD clinically by the presence of visuospatial dysfunction, but in clinical practice, bedside differentiation is quite difficult. A recent comparison of 23 patients with PD having PDD pathology and 28 patients with PD + AD pathology found that none of the following predicted dementia pathology: education, response to anti-Parkinson medications, history of hallucinations, Mini-Mental State Examination (MMSE) score, or Unified Parkinson Disease Rating Scale (a clinical rating system for PD stage and symptom severity).[21] This study suggests that it is difficult to distinguish PDD + AD and PDD on the basis of motor symptoms, clinical course, or basic memory testing. Ongoing biomarker research may be helpful in improving prevalence estimates of AD in the PD population and also identifying treatment candidates if effective neuroprotective treatments are discovered.

Reversible cognitive dysfunction in PD. A basic evaluation of any adult complaining of cognitive dysfunction demands assessment for "dementia mimics"—mood disorder/depression, thyroid disorder, CNS lesion (eg, stroke or tumor), B12 deficiency.[35] However, recent data suggest additional secondary causes of cognitive dysfunction may be particularly relevant in PD. Reversible cognitive dysfunction can be produced by the adverse effects of medications, acute infectious, or metabolic illness, and a sudden change in cognition (over days or weeks rather than months or years) should prompt an evaluation for reversible causes of dementia. Benzodiazepines, opioids, narcotics, antihistamines, and hypnotics can be associated with subacute/acute confusion and hallucinosis in individuals with PD and should be avoided. The temporal relationship between onset of acute/subacute cognitive dysfunction and use of any and total number of CNS acting medications should always be assessed and documented for patients with PD. When used chronically or in an additive fashion in a patient with PD, these medications can produce cognitive slowing that mimics the spectrum of cognitive dysfunction (from MCI to frank dementia).

Antiparkinsonism medications themselves may cause cognitive impairment that manifest as slowed thinking, decreased attention, disorientation, and hallucinosis as well. Members of the oldest class of antiparkinsonism medications, anticholinergic anti-parkinsonism medications (eg, selegiline, trihexyphenidyl, benztropine) are no longer commonly prescribed because (1) the amount of benefit they provide is modest compared to dopaminergic therapies and (2) several studies have demonstrated a dose-dependent negative effect of anticholinergic medications on cognitive function.[36-38] Although anticholinergic anti-Parkinson medication prescribing has declined substantially, physicians often fail to consider the anticholinergic effects of non-PD medications. Many common medications (eg, Selective Seretonin Re-uptake Inhibitors [SSRIs], digoxin) have direct or indirect anticholinergic potential, and total anticholinergic exposure has also been shown to directly affect cognitive performance in older adults. Efforts to increase physician awareness of these effects have produced several clinical tools to quantify anticholinergic burden (eg, the Anticholinergic Cognitive Burden Scale, ABC).[39] These bedside rubrics allow

Table 1. Guideline-Compliant Care for Diabetes in Parkinson Disease Compared to Other Medicare Populations.

Study First Author, Year (Number of Participants)	Medicare Beneficiary Population	Eligible Beneficiaries Receiving Recommended Care (%)	
		Glycosolated Hemoglobin Measurement	Diabetic Eye Examination
Willis AW, 2014 (n = 1 322 732)	Parkinson disease	18.6	22.4
Earle CC, 2004 (n = 18 699)	Colorectal cancer survivors	n/a	27.1
Asch SM, 2000 (n = 345 253)	African American	28.6	36.4
	White	37.2	43.9
	Residing in Health Provider Shortage Area (HPSA)	32.3	41.1
Schneider EC, 2001 (n = 10 782)	Poverty area	26.0	37.3
Pham, 2005 (n = 24 581)	Overall	55.9	47.9
Chang VW, 2010 (n = 36 122)	Obese	74.5	63.2

a clinician to quantify the anticholinergic exposure caused by common cardiac, psychiatric, and anti-Parkinson medications (most of which have lower anticholinergic alternatives) and will hopefully improve prescribing practices in older adults, including those with PD.

Preventable cognitive dysfunction in PD. The growth of treatments for early and advanced PD motor symptoms in the past 20 years has resulted in increased survivorship for PD. Clinical outcomes research for PD has traditionally focused on symptomatic therapies (such as medications for tremor, slowness, rigidity, shuffling gait) and disease-related outcomes (tremor severity, gait speed, disease-related quality of life), overlooking the other health needs of the patient with PD. With increasing age, especially in the United States, those at risk for PD are likely to have other coexisting medical conditions, including hyperlipidemia, diabetes, obesity, atherosclerotic vascular disease, atrial fibrillation, or have a personal history of myocardial infarction, transient ischemic attack. Advanced age, along with these comorbid conditions, place a patient with PD at increased risk of developing vascular dementia, particularly if patients with PD do not receive quality (guideline-adherent) comorbid and preventative care. To begin to understand the potential burden of preventable dementia in PD, from 2007 to 2009, we performed a retrospective cohort study of 1 322 732 Medicare beneficiaries > 64 years diagnosed with PD who also had diabetes. We calculated the proportion of eligible patients with PD receiving guideline-compliant diabetes monitoring in 1 calendar year. We found that few eligible patients with PD received yearly recommended care for diabetes, and guideline-compliant care in PD is lower than reported for other vulnerable groups measured using identical methods (Table 1).[40] Although future studies that focus on the quality of comorbid disease care in PD are needed, these data suggest that a measureable portion of secondary cognitive impairment in patients with PD is preventable.

Clinical Assessment of Dementia

The Movement Disorders Society Task Force has published practical clinical approaches to diagnosing PDD.[30,41] The minimum criteria for diagnosis of PDD are (1) diagnosis of PD based on the UK Parkinson Disease Society Brain Bank criteria, (2) PD developed prior to the onset of dementia, (3) MMSE score <26, (4) cognitive deficits severe enough to affect daily living, based on caregiver interview, and (5) impairment in $\geq$2 of the following: attention, executive function, visuospatial function, and memory. In practice, most patients with PD, or their care providers, have concerns/complaints about memory and cognitive function; therefore, memory testing and screening for dementia is an integral part of the patient with PD assessment. Unless actively ascertained, the initial symptoms of dementia—short-term memory complaints—are dismissed by patient, caregiver, and physician alike as simply "older age." This results in numerous missed opportunities to diagnose cognitive impairment in its earliest stage, when reversible and/or preventable components are most amenable to intervention.

Regular formal screening for cognitive impairment is the minimum standard of care for individuals with PD; American Academy of Neurology Guidelines recommend a formal evaluation of cognitive function no less than once per calendar year, and documentation of memory complaints at every visit.[42] Several clinical tools are available to meet this standard of care. The most commonly used tools for screening of dementia in PD are the MMSE, Montreal Cognitive Assessment (MoCA), and Dementia Rating Score II (DRS-II). An MMSE is a battery of 30 questions that can be completed within 5 minutes and is probably one of the most commonly used cognitive screening tests for dementia in the outpatient setting.[43] Ease and familiarity foster its widespread use among primary care physicians and nonneurology specialists; however, the sensitivity of MMSE for detecting cognitive and executive dysfunction in PD has been questioned.[44,45] A recent study demonstrated the original cutoff value <26 for MMSE has a 94% sensitivity for PDD, but the authors also proposed a diagnosis of PDD is reasonable when abnormalities are present in at least two cognitive domains in case of normal performance on MMSE.[46] Since the publication of level I screening guidelines for PDD by MDS,[41] many studies have evaluated the validity of the proposed checklist.[47,48]

The MoCA is a 30-point instrument that can be administered in 10 minutes.[49] The latest version of MoCA covers 8 important cognitive domains and is a good tool for diagnosis

of MCI. The MoCA has better sensitivity than MMSE for screening for dementia in PD because it is better able to detect MCI in the PD population.[49-52] Important domains of MoCA that make this tool a superior test for diagnosis of MCI when compared to MMSE are memory testing that includes more words, fewer learning trials, a longer delay before recall, higher-level language and executive function testing, and a more complex visuospatial processing. Many of these domains are mildly impaired in patients with MCI and MoCA has more detailed questions to identify this group of patients. Recently a cross-sectional multicenter study that administered the MoCA and MMSE to 305 patients with PD showed that the MMSE and MoCA together are practical and useful screening tests for the diagnosis of PDD in the office.[53]

The DRS-II) is a more detailed test for cognitive dysfunction in PD. The five different domains assessed by DRS-II are attention, initiation/perseveration, construction, conceptualization, and memory. The average time needed for completion of DRS-II is 20 to 30 minutes and can last longer in individuals with severe cognitive impairment.[54] Several studies have supported the use of the DRS-II because it has a very high sensitivity and specificity for assessing cognitive decline in PD.[55]

Given the length of time required by the DRS-II, a brief screening test that combines elements of the MMSE and MoCA has been recently developed and validated to identify dementia in PD in the outpatient setting. The PDD-Short Screen (PDD-SS) includes items that test immediate and delayed verbal memory, verbal fluency, clock drawing, and a brief questionnaire on cognitive and psychiatric (apathy, depression, hallucinations) symptoms. A score $\leq$11 on the PDD-SS produced high sensitivity (89.8%) and specificity (88.5%) for diagnosing PDD compared to the clinical gold standard tools. The PDD-SS requires only 4.8 to 6.9 minutes to administer, and a PDD-SS positive screen was not influenced by age, education, or PD severity (motor function).[56,57]

The Scales for Outcomes in Parkinson's disease–cognition (SCOPA-cog) is a PD-specific cognitive scale that has 10 items and 4 domains and requires 10 to 15 minutes to administer.[58] Although developed for the research setting,[58] SCOPA-cog can be a useful bedside screening or diagnostic tool. The main cognitive domains of SCOPA-cog test are memory and learning (cube test, 10-word recall, and backward digit span), attention (months backward, serial subtraction), executive function (motor planning, working memory, and verbal fluency tasks), and visuospatial function (figure assembly task). Because the SCOPA-cog includes specific assessments of executive function, it may be more sensitive to early cognitive decline than the MMSE.[59] Further, SCOPA-cog has superior reproducibility, greater internal consistency in PD than the MMSE.[58] A recent study applied MDS-PDD criteria to the SCOPA to establish cutoffs for a diagnosis of PDD, facilitating its use in clinical practice.[60] Optimal screening and diagnostic cutoffs were 24/25 and 17/18, respectively, with a suggested cutoff of 22/23 for maximum accuracy.

Dementia Treatment in PD

Exercise

Physical and cognitive exercises have beneficial effects on the cognitive reserves of the brain. Physical activity decreases brain injury from diabetes mellitus, hypertension, hypercholesterolemia, and obesity, reducing the impact of vascular dementia, and may also independently reduce the risk of neurodegenerative disease–associated dementia.[61-64] According to prospective cohort study of random sample of 864 elders in southeast Pennsylvania, the risk of incident MCI was lowest when physical and cognitive exercises were combined; this combination was associated with an 80% risk reduction in MCI.[65] However, when the 2 categories were studied individually, only physical activity had a significant effect on decreasing the incidence of MCI. Thus, physical activity can be considered at present to be a primary neuroprotective factor and cognitive exercise secondary protective measure.[65] Additionally, several studies of exercise in PD have demonstrated improvements in executive function, improved goal-directed behavior, and decision-making.[66] Improved frontal lobe function may be in addition to the known benefits of exercise on PD motor function and motor progression.[67] Future studies may seek to quantify the effects of exercise on long-term cognitive function and patient-centered outcomes (such as quality of life, ability to work) in patients with PD.

Pharmacotherapy

As shown in Table 2, there are several medications available to treat cognitive dysfunction in PD. Individuals with PD, even those who have not developed dementia yet, have severe deficits in cortical acetylcholine, and cholinergic deficit increases with the development of cognitive dysfunction.[68] Therefore, acetylcholinesterase inhibitors such as donepezil (Aricept) or rivastigmine (Exelon) represent rational restorative approaches to the pharmacological treatment of dementia in PD. Donepezil hydrochloride is the most widely used acetylcholinesterase inhibitor and treatment for dementia. Clinical trials have found modest improvement in cognition in patients with PD taking donepezil (5-10 mg/d), with few or mild adverse effects.[69,70] Several studies also support the efficacy of rivastigmine for the treatment of mild to moderate dementia in PD. A double-blind placebo-controlled study of rivastigmine dosed 3 to 12 mg/d showed improvements in performance on neuropsychiatric testing in PDD and improved behavioral symptoms, executive function, and attention with rivastigmine use.[68] Rivastigmine has the added benefit of reducing hallucinations (both visual and nonvisual), as shown by a 24-week double-blind placebo-controlled study.[71] However, nausea, vomiting, and increased tremor are the commonly reported side effects.

Galantamine (Nivalin, Razadyne, Razadyne ER, Reminyl, Lycoremine) works as a ligand for nicotinic acetylcholine receptors and also as an acetylcholinesterase inhibitor.[72] Open controlled trials of galantamine (8-16 mg/d) in 41 patients with PD and dementia compared to controls showed that patients treated with galantamine had better scores on multiple clinical

Table 2. Treatment of Dementia in Parkinson Disease.

Drug	Dosing Instructions	Side effects	Additional Benefits
Donepezil	• Initial: 5 mg orally qHS • Increase to 10 mg/d after 4-6 weeks if warranted	Nausea (20%), diarrhea, sleep disturbance (1%-10%)	
Galantamine	Immediate release • Initial: 4 mg orally every 12 hours • Increase by 4 mg/dose every 4 weeks to 8-12 mg orally every12 hours Extended release • Initial: 8 mg orally every morning • Increase by 8 mg/dose every 4 weeks to 16-24 mg orally every morning	Nausea (20%), diarrhea, drooling, nausea, dysuria, postural hypotension (1%-10%) Hepatic impairment: Moderate: (Child-Pugh score 7-9): do not exceed 16 mg/d Severe: do not use Renal impairment: Moderate: do not exceed 16 mg/dSevere (CrCl < 9 mL/min): do not use	
Memantine	Immediate release • Initial: 5 mg orally once daily • Increase by 5 mg orally every day every 1 week • Maintenance: 20 mg/d orally divided every 12 hours Extended release • Initial: 7 mg orally every day • Increase by 7 mg/d every 1 week • Maintenance: 28 mg orally every day	Generally well tolerated; may cause dizziness, confusion, headache, or increased tremor (1%-10%) Hepatic impairment: Severe (Child-Pugh C): caution Renal impairment: Severe: (CrCl 5-29 mL/min): do not exceed 14 mg/d (extended release) or 5 mg twice a day (immediate release)	Reduction in axial motor signs, dyskinesias, motor fluctuations
Rivastigmine	Oral • Initial: 1.5 mg orally every 12 hours • Increase by 1.5 mg/dose every 4 weeks • Maintenance: 1.5-6 mg orally every 12 hours Transdermal • Initial: apply 4.6 mg every 24 hours • Increase to 9.5 mg every 24 hours after a minimum 4 weeks (if tolerated); increase to 13.3 mg patch if warranted	Nausea, vomiting, worsening tremor, headache, diarrhea (1-10%) Mild to moderate hepatic impairment: not to exceed 4.6 mg every 24 hours Low body weight (<50 kg): titrate carefully and monitor patients for toxicity (eg, nausea, vomiting)	Reduction in hallucinations (visual and nonvisual)

cognitive assessment tools (eg, MMSE, neuropsychiatric inventory, frontal assessment battery) and have significant improvements in hallucinations, anxiety, sleep disturbance, apathy, daily activity, and reduced caregiver stress. Freezing and falls decreased as well. However, 30% of patients had side effects including nausea, drooling, increased tremor, postural hypotension, and dysuria.[73]

Memantine (Namenda, Axura, Akatinol, Ebixa, Abixa, Memox) is an N-methyl-D-aspartate receptor inhibitor. Memantine has been demonstrated to modestly improve attention and episodic memory in PDD and DLB in placebo-controlled randomized clinical trials (RCTs).[74] A 22-week double-blind RCT of individuals with PDD also found modest improvements in goal attainment, caregiver burden with memantine treatment.[75] Improvement in axial motor symptoms (neck stiffness, forward-leaning stance) and dyskinesias (fluctuating chorea or dystonia) have also been observed in memantine-treated patients, but the broader benefit of using memantine for these symptoms alone is unclear.[76,77]

Cognitive Therapy

The majority of studies that tested the interventions for cognitive therapy have resulted not only in cognitive improvement but also in activities of daily living, including driving and safety. Computerized brain training and nonphysical leisure activities are among different interventions that have been studied.[78] A single blind, single site, controlled trial used speed of processing training (SOPT) formatted for self-administration by older adults with exercises translated into a gaming format. Individuals in the active arm of this study had significant improvements in the speed of processing. However, of note, the control group also showed some improvements.[79]

Neuromodulation

Repetitive transcranial magnet stimulation (rTMS) is a noninvasive tool that has been used to modulate brain plasticity. It has been tested as a treatment for many neurological conditions including migraine headache, mood disorders, and strokes.[80-82] The evidence of rTMS used in the treatment of PDD is growing, but more data are needed to support adaptation into routine clinical practice. A small but randomized crossover study (complete with a sham procedure) of patients with PD who received active rTMS at the inferior frontal gyrus showed significant improvements in all subsets of Stroop test.[83] Another study from the same laboratory found patients who received rTMS (vs sham stimulation) at right and left dorsolateral

prefrontal cortex demonstrated statistically significant improvements in the total problem-solving time.[84] These initial data are encouraging, and future studies may demonstrate the ability of rTMS to produce clinically meaningful effects on cognitive function of patients with PD.

Conclusion

The changing demographics of the US population will place more individuals at risk of PD than ever before, and improved treatments for PD have led to significant gains in survivorship, highlighting the need for clinicians to become capable of caring for patients with PD. Cognitive dysfunction, as the most common and probably most devastating nonmotor symptom of PD, results in a spectrum of deficits ranging from MCI to severe dementia. The development of dementia in PD also increases the likelihood of nursing home placement, which results in higher health-related costs and increased caregiver burden.[85-87] We have recently shown that dementia is one of the important risk factors for nursing home placement (AOR 4.06, 95% CI 4.00-4.12) in a large cohort of Medicare beneficiaries with diagnosis of PD.[87] Dementia is also an independent predictor of mortality in patients with PD.[86] As a result of several longitudinal studies, the theory that all patients with PD who survive long enough will also have dementia is widely accepted now. Although it is difficult to predict the onset of cognitive decline when a patient is diagnosed with PD, those who have the gait dominant motor phenotype, sleep disorders, dysautonomia, MCI, specific gene haplotypes, and comorbid hypertension are more likely to develop dementia earlier.

Recent clinical epidemiological data highlight the potential burden of reversible and preventable cognitive dysfunction in individuals who have PD as one of their comorbidities. Recognizing and reducing the impact of reversible cognitive dysfunction is an important first step in caring for a patient with PD with suspected dementia. Preventing early cognitive dysfunction due to liver, renal, vascular disease requires recognition of the need to provide guideline-adherent care to individuals with mild to moderate PD, rather than focus care exclusively on PD motor symptoms.

Many clinical assessment tools scales are available for rapid outpatient cognitive assessment of patients with PD, and current guidelines recommend an annual cognitive examination. Multiple different pharmacological treatments are now available for dementia in PD, and all provide modest symptomatic benefit. Additionally, treatment of cognitive dysfunction includes counseling patients with PD and their caregivers on the potential neuroprotective effects of exercise.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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