Cognitive Impairment in Parkinson's Disease and Dementia with Lewy Bodies: A Spectrum of Disease

Rachel Goldmann Gross Andrew Siderowf Howard I. Hurtig

Parkinson's Disease and Movement Disorders Center, Department of Neurology, University of Pennsylvania Health System, Philadelphia, Pa., USA

Key Words

Parkinson's disease • Dementia • Cognitive impairment • Dementia with Lewy bodies

Abstract

Parkinson's disease (PD) is classically thought of as a movement disorder characterized by tremor, rigidity and postural instability. Nevertheless, there is growing recognition of prominent cognitive impairment in PD and related disorders, which is responsible for substantial disability in these patients. This review will focus on cognitive impairment associated with Lewy body pathology, including PD with dementia (PDD) and dementia with Lewy bodies (DLB). We will review the epidemiology, clinical evaluation, underlying mechanisms and treatment of cognitive impairment in these patients. Despite differences between PDD and DLB, there is clinical, neuropathological and radiological overlap between these disorders, supporting the view that they represent a spectrum of disease. These observations suggest that common targets for diagnosis and treatment of these disorders can be identified.

Copyright © 2008 S. Karger AG, Basel

The Clinical Spectrum of Lewy Body Disorders

In his seminal and classic description of the neurologic disorder that now bears his name, James Parkinson described in timeless detail the physical features of 'paralysis agitans' in 6 patients (3 examined, 3 observed from a distance on the streets of London), and he remarked that there was 'an absence of any injury to the intellect' [1]. However, time has proved that this observation by Parkinson was wrong, in part because of the notably small sample size from which he derived his conclusions. Moreover, there is growing evidence that cognitive impairment is not only common in Parkinson's disease (PD), but is a major source of disability late in the course of illness. As an example, Weintraub et al. [2] have shown that cognitive impairment and depression, its psychiatric comorbid companion, contribute significantly to functional disability in PD after controlling for overall disease severity. In addition, cognitive symptoms in patients with PD are associated with more rapid disease progression [3], increased frequency of nursing home placement [4], greater caregiver burden [5], reduced quality of life [6] and increased mortality [7].

This review will focus on the array of cognitive disorders associated with Lewy body (LB) pathology, including PD with mild cognitive impairment, PD with dementia (PDD) and dementia with LB (DLB), diagnoses characterized by the combination of motor features of par-

Table 1. PDD and DLB clinical profiles

Neuropsychological performance almost identical
Psychiatric symptoms the same
Both have REM behavior disorder
Parkinsonism more symmetrical and tremor less in DLB
Neuroleptic sensitivity less in PDD
Levodopa response not as robust in DLB
Similar response to cholinergic treatment

kinsonism and cognitive deficits. It is debated in the literature whether PDD and DLB are distinct entities or represent a spectrum of motor, cognitive and behavioral impairment [8–10]. The current consensus on the clinical diagnosis of these entities classifies them according to the relative timing of the onset of motor and cognitive symptoms, using the ‘1 year rule’. That is, the diagnosis of DLB is made when cognitive symptoms appear within 1 year of the onset of motor symptoms, whereas the diagnosis of PDD is made when cognitive symptoms begin more than 1 year after onset of motor symptoms [11].

The cognitive and psychiatric symptoms of DLB and PDD are essentially the same (table 1). Both have fluctuating abnormalities of cognition (confusion, disorientation, delusions), and well-formed visual illusions and hallucinations [9, 11, 12]. Other features common to PDD and DLB include autonomic abnormalities, REM sleep behavioral disorder, sensitivity to neuroleptic medications, repeated falls and unexplained episodes of loss of consciousness [9]. Moreover, patients show similar neuropsychological profiles, characterized by prominent executive and visuospatial dysfunction, as well as fluctuating levels of alertness and cognition [13–15]. In addition, neuropathological changes in PDD and DLB tend to be similar or even indistinguishable [8–10].

On the other hand, some authors have reported demographic, clinical and pathological differences between patients with PDD and DLB. For example, PDD tends to affect younger patients than DLB [16]. Patients with DLB may have more executive dysfunction and psychiatric symptoms than patients with PDD [8]. PDD patients may have more prominent parkinsonism, while patients with DLB are more likely to have pronounced gait abnormality, postural instability and decreased levodopa responsiveness [8, 11]. Some reports have also demonstrated differences in the amount and distribution of pathological changes in PDD versus DLB patients [8].

Overall, the differences between DLB and PDD tend to be small and inconsistent across studies. Indeed, PDD

and DLB are increasingly thought to be part of a spectrum of disease characterized by overlapping motor, neuropsychiatric and neuropathological abnormalities. As such, the more expansive term ‘LB dementia’ has been coined to encompass patients with PDD and DLB [9], highlighting a common pathology and the need to investigate shared targets of diagnosis and treatment [9].

Epidemiology and Risk Factors for Dementia in PD and DLB

Historically, estimates of the frequency of dementia in PD have varied widely. Prevalence rates in the literature range from 3 to 80%, the variability being related to population differences, survey biases and dementia criteria employed [17]. A review of 27 epidemiologic studies found an average prevalence of 40% [18]. However, prevalence of dementia in cross-sections of PD patients does not address the potential impact on an individual over the course of the disease. PDD affects a majority of patients over a long term. In a study of 224 patients with PD, Aarsland et al. [19] found dementia rates of 26% at baseline, 51% at 4 years and 78% at 8 years. After Alzheimer’s disease (AD), DLB is the second most common type of degenerative dementia in older people. In non-population-based studies, estimates for prevalence of DLB varied between 3.0% [20, 21] and 26.3% [22] of all demented cases over the age of 65 years. This is similar to estimates from autopsy series, which have ranged between 15 and 25% [21, 23].

Identifying risk factors for dementia in PD is somewhat artificial, since many PD patients have evidence of cognitive symptoms at the time of diagnosis. Using a comprehensive battery, Muslimovic et al. [24] found that 24% of patients with newly diagnosed PD had cognitive impairment (defined as poor performance on at least 3 cognitive tests). Foltynie et al. [25] found that 36% of patients in a population-representative cohort of 239 newly diagnosed PD patients had evidence of cognitive impairment. Thus, even at the time of diagnosis, cognitive features can be identified in a high proportion of PD patients. Nonetheless, risk factors for dementia in PD have been identified. The best established is the association between advanced age and development of cognitive impairment. This relationship is largely due to the increased incidence of the clinical features and neuropathologic changes of dementia over the life span. Perhaps surprisingly, duration of PD has not been consistently associated with the development of dementia, likely because age is

the more significant risk factor for dementia [26, 27]. There may also be a relation between dementia and later age of disease onset [24]; however, this also has not been consistently demonstrated [28]. Among environmental exposures, smoking has been associated with increased risk of dementia in PD [29]. APOE genotype, which is consistently associated with risk of AD, does not appear to be a risk factor for PDD [30].

Several clinical features, notably hallucinations at baseline evaluation, have been associated with higher risk of subsequent PDD [19, 31]. In addition, dementia is more likely to develop in patients with early mild impairments on neuropsychological testing, analogous to the risk of developing AD in patients with mild cognitive impairment [32]. Earlier and more widespread neuropathological changes likely account for this relationship. As will be discussed below, there are associations between cognitive impairment and the amount and distribution of various types of pathological changes in the brain [32, 33].

Some reports have shown that dementia correlates with greater severity of motor impairment [28]. This observation suggests common pathologic mechanisms underlying cognitive and motor difficulties in the LB dementias, and that dopaminergic drugs should improve cognition as they do motor deficits. Moreover, there are correlations between cognitive impairment and types of motor deficits including rigidity and bradykinesia [19, 27], early tremor [34], severe axial symptoms such as postural instability and gait impairment [24, 27] and speech impediments [24]. The association between dementia and motor deficits less responsive to dopaminergic pharmacotherapy (for example postural instability, speech and gait) suggests that impaired cognition in the LB diseases is related to abnormalities of other neurotransmitter systems [24].

Cognitive and Behavioral Impairments in PDD and DLB

In patients with PDD and DLB, the most consistent neuropsychological deficit is frontal/executive dysfunction. Patients show poor attention, planning and inhibition, as well as slowed information processing. Day to day, patients have difficulty multitasking and take longer to complete simple or familiar tasks. These problems often interfere with the ability to help at home or maintain employment [17]. Neuropsychological testing reveals difficulty with category fluency, digit span, action sequencing, problem solving, rule deduction, set shifting and sus-

tained attention. In a study of 115 patients with newly diagnosed PD, Muslimovic et al. [24] demonstrated that differences in cognitive performance between PD patients and controls were mainly explained by measures of executive function and immediate memory. Executive dysfunction is likely due to compromise of connections between the basal ganglia and frontal cortex [17, 32]. However, it is important to keep in mind that motor deficits including bradykinesia, loss of fine motor control and tremor may hinder performance on any cognitive task, particularly those measuring executive function [17].

Patients with PDD and DLB also have prominent perceptual and visuospatial deficits. Patients may complain of a vague sense of 'not seeing well', and may have trouble reading, following maps and navigating in familiar settings [17]. Mosimann et al. [35] showed that patients with PDD and DLB matched for dementia severity had similarly impaired visual perception relative to control subjects and nondemented PD patients. Visuo-perceptual difficulty in these patients was attributed to cortical cholinergic deficits, LB in cortical visual areas and perhaps retinal changes related to disruption of dopaminergic processes [35]. In contrast, Muslimovic et al. [24] argued that their measures of visuospatial processing depended on executive functions (such as spatial reasoning and strategizing) and felt that impaired performance on visuospatial tasks may not reflect an independent deficit in this cognitive domain. The difference here is likely due to task selection: in the latter study, participants were asked to perform tests requiring more sophisticated processing of visual information such as spatial reasoning and strategizing more susceptible to interference by executive dysfunction.

Language tends to be relatively well preserved in patients with PDD and DLB. Patients usually have problems with speech as opposed to language function. For instance, patients with PD often have slow or sparse speech. Impaired motor function involving the articulatory apparatus leads to dysarthria, reduced volume, poor articulation and abnormal prosody. Although profound aphasia is rare in PD, more subtle language disturbances can be seen. For instance, patients with PD have greater difficulty processing grammatically complex sentences (for example, with object-relative center-embedded clauses) than grammatically straightforward sentences (for example, no embedded clauses or subject-relative clauses). While this difficulty has been attributed to impaired grammatical processing, there is evidence that the difficulty with complex sentences is due to executive resources including attention allocation and processing speed

[36]. Lee et al. [36] showed that difficulty with object-relative embedded clauses was correlated with executive measures including reverse digit span and category fluency. Grossman et al. [37] showed that relative to control subjects, patients with PD had greater reduction in sentence comprehension when asked to perform a concurrent task.

Most patients with PD ultimately develop memory impairment, although memory tends to be relatively spared early on. At times other common neuropsychiatric problems such as inattention, depression and apathy give the impression of impaired memory. Patients with PD have particular difficulty with tests of recall, suggesting difficulty retrieving information. In keeping with this observation, patients often benefit from cueing, a cognitive strategy which bolsters information retrieval and which tends to be less helpful in patients with AD with compromised memory encoding. It is not surprising that patients with PD would have difficulty with information retrieval, as this process depends on intact allocation of attentional resources, typically considered a frontally mediated function.

Moreover, it is common for patients with PDD and DLB to have fluctuating levels of alertness and cognition [14, 15]. This variability is, in fact, one of the defining features of DLB [11]. Fluctuations are exacerbated by changes in dopaminergic drug levels throughout the day. However, some of the fluctuations in alertness and cognition occur over the course of days to weeks, suggesting a process separate from medication effect [17]. It is also important to assess for common causes of variable cognition in elderly patients, including medication effect, occult infection, electrolyte abnormalities and subdural hematoma.

Early in the course of PD, patients may have cognitive deficits manifest only on careful neuropsychological testing. Muslimovic et al. [24] demonstrated executive and memory impairment in 115 patients with newly diagnosed PD. Of note, most patients considered themselves independent, suggesting that early on cognitive impairment may be subtle and of minimal functional consequence [24]. Of interest, there was no significant difference on the Folstein Mini-Mental State Exam (MMSE) between patients and controls, underscoring the importance of tests with greater focus on executive function (which is not well represented in the MMSE) early in the disease process when orientation, language and memory are relatively well preserved [17].

Dopaminergic medications, with their variable effects on alertness and cognition, may complicate neuropsychological

assessment of individuals and groups of patients with LB dementia. Muslimovic et al. [24] showed no significant difference in levodopa equivalent dose (calculated by pooling dopaminergic drugs) in PD patients with and without cognitive impairment. The authors concluded that the cognitive deficits they observed in patients with PD could not be attributed to dopaminergic therapy [24]. However, assessment of cognitive deficits in individual patients in the office is likely influenced by the use of dopaminergic drugs; on- and off-state fluctuations could certainly affect patients' performance on tasks requiring alertness, sustained attention and motor response.

Another potential confounding factor is depression, which is extremely common in PD and well known to cause a 'pseudodementia' in many patient populations. Some studies have shown that cognitive impairment is exacerbated by depression and apathy [38, 39]. Uekermann et al. [39] showed greater impairment of working memory, concept formation and verbal fluency in depressed PD patients relative to nondepressed PD patients matched for disease severity and MMSE score. However, Muslimovic et al. [24] demonstrated that the pattern of cognitive deficits in patients with newly diagnosed PD was not altered by controlling for depressive symptoms and argued that cognitive impairment in their patients was not explained by depression. Although depression seems to exacerbate cognitive dysfunction, mood disorder does not seem to account in full for neuropsychological deficits in patients with LB dementia.

Finally, there are notable differences in the neuropsychological profile of patients with LB dementia versus those with AD, the most common type of dementia (table 2). The presence of visual hallucinations at presentation is the most specific factor in differentiating between PDD and AD [40]. However, visual hallucinations are present in a minority of DLB patients (22%) early in the disease. In PDD and DLB, there are prominent abnormalities of executive function, mood and visual perception, while memory loss is typically a later finding. In contrast, patients with AD show early and more severe memory impairment with later development in some patients of executive and language dysfunction. For instance, Aarsland et al. [13] showed that patients with PDD and DLB were less impaired on memory tasks and had more difficulty with executive measures relative to patients with AD. Mosimann et al. [35] found more severe visuo-perceptual deficits in patients with PDD and DLB relative to those with AD. Ballard et al. [14] demonstrated greater cognitive fluctuation in these patients compared

Table 2. Comparison of cognitive profiles of PDD/DLB and AD

Cognitive domain	PDD/DLB	AD
Frontal-executive	Prominent and early deficits; PD patients without dementia may have impairments in sustained attention and set shifting	Later and less severe than PDD/DLB
Memory	Retrieval memory impaired, but encoding memory less affected	Early memory complaints are common; both encoding and retrieval affected; inability to form new memories is common
Language	Complaint of word finding difficulty common, but language problems are not prominent on formal testing	Language problems including paraphasic errors are common
Visuospatial	Impairments often found on formal testing; may be most common impairment in formal testing	Deficits present but less pronounced than in PDD/DLB
Psychosis/behavioral disturbance	Formed visual hallucinations common and may occur without dopaminergic therapy	Visual hallucinations unusual; suspiciousness and disinhibition more common

to those with AD. In general, though, cognitive differences between patients with LB dementia and those with other types of dementias (such as AD, vascular dementia or frontotemporal dementia) are most remarkable in the early stages of disease. The neuropsychological distinctions, irrespective of cause, lessen as cognitive impairment becomes progressively severe.

Neuropathology of PDD/DLB and Potential Biomarkers

The histopathological hallmarks of PD are the intracytoplasmic neuronal inclusions (the LB) and inclusions confined to neuronal processes (axons and dendrites) known as Lewy neurites (LN). Both contain the presynaptic protein α -synuclein, the discovery of which in mutated form a decade ago [41] has led to the coinage of the term synucleinopathy to describe the process by which the protein becomes misfolded and forms pathologic aggregates. PD has been traditionally defined by the presence of neuronal degeneration and LB in the substantia nigra of the mesencephalon, but LB and LN have been described more recently [42] in the basal forebrain, raphe nuclei, locus ceruleus, Edinger-Westphal nucleus, the olfactory bulb, autonomic ganglia, dorsal motor nucleus of the vagus, the limbic system, hippocampus and the cerebral cortex. According to Braak et al. [42], the Lewy pathology begins preclinically in the lower brainstem and olfactory bulb, then ascends the neuraxis in an orderly fashion to the substantia nigra, at which point motor symptoms first appear. Further ascent to the cerebral cor-

tex is associated with the emergence of significant cognitive impairment. Ultimately, according to the Braak staging system, this wide distribution of Lewy pathology accounts for the motor, neuropsychiatric, neuro-ophthalmologic and autonomic abnormalities seen clinically in patients with PD and eventually PDD.

There is debate in the literature regarding the type of pathological changes associated with cognitive impairment in PDD and DLB. Hurtig et al. [33] at the Center for Neurodegenerative Research at the University of Pennsylvania studied the brains of 42 patients with PD, approximately half of whom had dementia. The authors found that cortical LB (CLB) were more sensitive and specific correlates of dementia (91 and 90%, respectively) than amyloid plaques, neurofibrillary tangles and dystrophic neurites. The authors also found a correlation between the amount of CLB and severity of dementia, although this finding has not been universally accepted, since CLB can be found in patients with little or no cognitive impairment [43]. Moreover, there are no well-defined criteria for the number of CLB required for a neuropathologic diagnosis of PDD or DLB. More recently, Ballard et al. [44] have reported that the intensity of CLB pathology is inversely correlated with the duration of parkinsonism before the onset of dementia, and they argue that their data support the concept of a continuum of the spread of LB pathology rather than an arbitrary cutoff between DLB and PDD, as advocated by the clinical consensus criteria [11].

Some authors have suggested that a synergistic interaction between LB and Alzheimer-type pathology contributes to the pathogenesis of dementia in some patients

with DLB and PDD despite the lack of significant AD pathology in the majority of DLB/PDD brains that have been studied [33, 45, 46]. None of the reports on this subject has presented convincing evidence that coexisting Alzheimer pathology influences the clinical phenotype of either DLB or PDD.

The role of the LB in the pathogenesis of PD and DLB remains controversial, although the concept is evolving that the LB forms as a default protective response to the failure of the cell's ubiquitin-proteosomal waste disposal system to clear the cell of pathologic aggregates of synuclein and other byproducts of the process of neurodegeneration [47]. Other intracellular mechanisms that can potentially back up an overloaded ubiquitin-proteosomal system have also been identified, most recently the lysosomal-mediated process known as autophagy. The recent finding that the immunosuppressant drug rapamycin can induce autophagy and rescue neurons in an animal model of PD suggests a possible therapeutic role for the autophagy system in PD [48].

Some authors have tried to distinguish PDD from DLB using differences in amount or distribution of neuropathological changes. For instance, LB have been found to be more frequent in the temporal lobes in DLB, which has been associated with the early and prominent well-formed hallucinations seen in this disorder [8]. In general, however, there are no substantial pathological differences between patients with PDD and DLB at the time of autopsy. While this observation may be biased because patients' brains are typically examined at the end stage of disease, it does support the conceptualization of PD, PDD and DLB as a broad clinical spectrum of motor and non-motor abnormalities with a common underlying pathology.

Neurochemical changes in PDD and DLB have also been extensively studied. Most work has focused on dopamine transmission in frontostriatal circuits, based on the notion that a common abnormality could explain both motor and nonmotor symptoms of the LB diseases. In particular, abnormal dopamine transmission between basal ganglia and the prefrontal cortex may account for executive dysfunction in patients with PDD and DLB, although this hypothesis is undermined by the failure of cognitive deficits in PD to respond to dopaminergic therapy, suggesting that other neurochemical abnormalities are responsible.

Cell loss in the raphe nuclei around the aqueduct of Sylvius and in the locus ceruleus is the likely cause of the well-documented depletion of serotonin and norepinephrine, which may explain abnormalities of mood, lev-

el of alertness and attention in DLB and PDD [32]. Moreover, loss of cholinergic neurons in the nucleus basalis is a common finding in DLB and PDD and contributes significantly to deficits of memory, attention, level of alertness, learning and possibly the mysterious fluctuations [14].

Recent advances in brain imaging have helped to clarify some of the pathological differences among the various dementing syndromes. Imaging with MRI and radionuclide isotopes (positron emission tomography, PET, and single photon emission computed tomography, SPECT) has made it possible to identify amyloid deposits, particular patterns of atrophy and metabolism, depletion or alteration in the supply of neurotransmitters and the localization of anatomic regions that are activated during the performance of specific motor and cognitive tasks. For instance, functional MRI studies have shown decreased activation in frontostriatal areas during a working memory task in patients with PDD that is different from patients with PD [49].

Cognitive processing is increasingly recognized to occur in multiple interconnected brain regions, which function as a network to generate particular behaviors. It is therefore essential to develop new methods of brain imaging to demonstrate the anatomic and functional correlates of these cognitive connections. To this end, Huang et al. [50] used PET to study nondemented PD patients who were performing executive and memory tasks to identify a 'metabolic network', characterized by hypometabolism in frontal and parietal association areas and by increased metabolism in the cerebellar vermis and dentate nucleus. Of note, this metabolic network was not altered by dopaminergic drugs or subthalamic nucleus deep brain stimulation (DBS), while these interventions did influence the metabolic pattern associated with performance of purely motor tasks. This observation provides further support for the notion that cognitive impairment in PDD and DLB is at least partially mediated by neural circuits separate from the dopaminergic frontostriatal circuitry associated with motor function [50].

Although understanding of the pathological and neurochemical substrate for PDD and DLB is likely to produce clinically useful biomarkers, there remains unmet need for such measures (table 3). Chemical biomarkers that have utility in AD, such as measurement of tau and amyloid in the cerebrospinal fluid, have not yet proved useful in the diagnosis of PDD, but are the subject of further study [51]. More recently, biomarkers based on α -synuclein aggregates have been proposed [52], as have patterns of RNA expression that can be measured in routine-

Table 3. Potential biomarkers for PDD and DLB

Status	
<i>Biochemical (serum)</i>	
α -Synuclein levels and isoforms	Assays exist as research tools, moderate specificity and sensitivity for PD vs. controls; not tested in PDD or DLB
Gene expression profiling	Assays exist as research tools, moderate specificity and sensitivity for PD vs. controls; not tested in PDD or DLB
<i>Biochemical (CSF)</i>	
β -Amyloid	Assays exist as research tools; levels reduced in AD patients; levels appear normal in PDD and DLB patients
Tau	Assays exist as research tools; levels elevated in AD patients, but are normal in PDD and DLB patients
<i>Imaging</i>	
Dopaminergic imaging (fluoro-dopa PET and SPECT imaging) of the dopamine transporter with various ligands	Abnormal in PDD and DLB; normal in AD; correlation between progression of cognitive symptoms and change in imaging is not known
Cholinergic imaging	Imaging with acetyl choline analogues shows substantial loss of cholinergic innervation in PDD and DLB (greater than AD)
Amyloid imaging	Early studies suggest that imaging of amyloid deposition in PDD and DLB with Pittsburgh compound B (PIB) is similar in magnitude and distribution to that seen in AD. PIB binding in PDD is known
<i>Sensory testing</i>	
Olfactory testing (UPSIT, olfactory threshold, etc.)	Abnormal in PDD and DLB, also abnormal in AD
CSF = Cerebrospinal fluid; UPSIT = University of Pennsylvania Smell Identification Test.	

ly collected blood samples [53]. However, both of these modalities require further validation, and their utility in distinguishing PD from PDD and DLB or LB disorders from other causes of dementia has not been studied.

As noted above, functional and molecular imaging has the potential to capture in vivo neurotransmitter deficits in PDD and DLB. Both PET studies using 18F-fluorodopa and SPECT studies using a range of ligands that bind to the dopamine transporter (DAT) have been shown to identify dopaminergic deficits in PD [54, 55]. A growing body of literature shows that these same dopaminergic deficits can be found in PDD/DLB and that these imaging modalities may be used to differentiate LB disorders from AD. Imaging of the DAT in the striatum shows subtle differences between PD and DLB, with PD patients showing greater side-to-side asymmetry and DLB patients showing relatively greater denervation of the caudate nucleus [56]. Functional imaging of the cholinergic system has shown substantial cholinergic denervation in PDD patients [57]. More recently, amyloid im-

aging in DLB patients has shown substantial deposition, comparable to patients with AD [58].

Olfactory function may also have a role as a biomarker for PDD and DLB. A comparison between measurement of olfaction and DAT imaging showed that the magnitude of olfactory loss correlated highly with DAT imaging in patients with early PD [59]. Studies have also shown olfactory deficits in DLB patients [60]. However, patients with AD have similar olfactory deficits, and the main use of olfactory testing may be to identify nonneurodegenerative causes of dementia, such as multi-infarct state, that have no impairment of olfaction.

Clinical Management of Cognitive and Neuropsychiatric Features of PDD/DLB

Treating cognitive impairment in PDD and DLB presents substantial challenges for the clinician (table 4). Frequently, therapies that benefit nonmotor symptoms

Table 4. Symptomatic treatment of PDD/DLB

Symptom	Treatment	Comment
Cognitive impairment	Cholinesterase inhibitors (rivastigmine, donepezil, galantamine)	Rivastigmine is FDA approved for treatment of cognitive symptoms in PDD
	Memantine	Evidence for efficacy in moderate to severe AD; no direct evidence of efficacy in PDD/DLB
Psychosis	Clozapine	Regular blood monitoring is required due to risk of agranulocytosis; common side effects are drowsiness and sialorrhea
	Quetiapine	Recent trials raise questions about efficacy; side effects similar to clozapine, but does not require blood monitoring
Decreased attention/ daytime somnolence	Methylphenidate	Avoid dosing in late afternoon and evening
	Modafinil	Avoid dosing in late afternoon and evening

negatively impact motor function, and vice versa. This problem is most evident in the case of motor and psychiatric symptoms in patients receiving dopaminergic medications. While dopaminergic medications may improve motor symptoms, there is also the potential to worsen visual hallucinations and paranoid or delusional thinking. When embarking on a treatment plan, it is important to discuss with patients and caregivers which symptoms are most disabling and therefore a priority to address [17, 61]. It is also essential to review patients' medications for drugs that exacerbate cognitive impairment and offer marginal clinical benefit, such as narcotics or anticholinergics.

The benefit of dopaminergic drugs for motor symptoms in typical PD is well established. Clinically, patients with PD and DLB can have worsening of psychiatric symptoms such as psychosis and impulsivity with dopaminergic drugs [17, 62], but the impact of these medications on cognitive function is unclear. Indeed, patients have shown stable, improved or worsened cognitive dysfunction with dopaminergic agents [17]. Molloy et al. [63] studied the effect of levodopa on alertness, verbal recall, reaction time and accuracy in patients with PDD and DLB both at the time of a levodopa challenge and after 3 months of chronic therapy. Acutely, there was increased cognitive fluctuation. Treatment with levodopa did not adversely affect cognition over 3 months of use [63].

Another therapeutic approach is DBS, which has become an important treatment modality for motor symptoms in patients with PD. Neuropsychological evaluations in patients treated with subthalamic nucleus DBS have shown decreased performance on frontal measures, including verbal fluency, postoperatively. Contarino et al. [64] studied cognitive performance in 26 patients with

PD who underwent bilateral DBS of the subthalamic nucleus, 11 of whom were assessed 5 years after surgery. At 5 years, there was a significant decline in verbal fluency and abstract reasoning. No patient developed dementia as defined by the DSM-IV, suggesting that the observed cognitive decline did not impact patients' ability to perform activities of daily living [64]. Of note, this study did not include PD patients who did not undergo DBS to control for disease-related deterioration in frontal function [64].

As discussed above, abnormalities in neurotransmitters in addition to dopamine contribute to cognitive deficits in PDD and DLB. Decreased cholinergic transmission has been shown to correlate with executive dysfunction and hallucinations [65, 66]. For this reason, there have been several investigations of acetylcholinesterase inhibitors (mainly donepezil and rivastigmine) in patients with PDD and DLB [61, 67–70]. Acetylcholinesterase inhibitors have been shown to improve global measures of cognitive function (such as the MMSE), as well as attention, executive function, cognitive fluctuation and hallucinations. Adverse effects of acetylcholinesterase inhibitors include somnolence and gastrointestinal distress. There are also disparate reports regarding the effect of acetylcholinesterase inhibitors on parkinsonism, including rare cases of increased motor deficit associated with these drugs [71].

Psychotic symptoms such as visual hallucinations and delusions are frequent in PDD and DLB and can be seen even in the absence of dopaminergic therapy. The most efficacious treatment for these psychotic symptoms is low-dose clozapine (up to 50 mg per day) [72]. The main side effects of clozapine are somnolence and increased

saliva, but it does not worsen parkinsonian signs. However, use of clozapine is associated with the rare occurrence of agranulocytopenia, and regular blood monitoring is required when clozapine is prescribed. Quetiapine (at doses from 25 to 200 mg per day) is also used as a treatment for psychotic symptoms in PDD and DLB. Data from open studies suggesting the effectiveness of quetiapine have not been confirmed in randomized controlled trials [73]. Antipsychotic medications with greater dopamine-blocking properties, including the newer atypical neuroleptics (other than clozapine and quetiapine) should not be used in PDD or DLB patients.

Neuropsychiatric symptoms including depression, drowsiness, anxiety and apathy may also complicate PDD and DLB. For all these problems, symptom recognition is crucial, as these features are often overlooked in the face of major motor and cognitive impairments. Although there is a scant evidence base for treating these problems specifically in the case of PDD or DLB, standard therapies may be reasonably applied to patients with LB disorders. Stimulants such as modafinil and methylphenidate can be used to treat drowsiness and apathy. Antidepressants including selective serotonin reuptake inhibitors, mixed catecholamine reuptake inhibitors, and tricyclic antidepressants may be used in PDD and DLB patients. However, tricyclics with significant anticholinergic properties should probably be avoided.

Conclusion

This article was intended to describe the cognitive profiles of patients with PDD and DLB and to review the underlying mechanisms, clinical evaluation and management of cognitive deficits. What has been learned from clinical, pathological and radiologic studies has in-

formed the debate over whether PDD and DLB represent distinct disorders. Overall, the similarities between these entities seem to outweigh the differences. Maintaining a distinction between PDD and DLB may be helpful clinically, as management approaches may differ for patients with prominent motor dysfunction versus those with prominent dementia. However, conceptualizing PDD and DLB as variations on a single disease with a common underlying mechanism is valuable for the pursuit of biomarkers for diagnosis and targets for treatment.

The profound impact of cognitive impairment on patients' functional status and long-term prognosis underscores the need for more comprehensive clinical assessments. It is essential that patient assessments evaluate both motor and nonmotor function. Neuropsychological batteries should feature tests of executive and visuospatial function, given the prominence of these deficits in PDD and DLB. Additionally, functional status, caregiver burden and quality of life should be formally assessed. This information would assist with diagnosis, as well as guide treatment strategies and recommendations about level of care. Moreover, these items are essential outcome measures for clinical trials in this patient population.

Another important goal is improved premortem diagnosis of patients with LB dementia. Of particular value are noninvasive imaging techniques that can distinguish these patients from those with AD, vascular dementia and other neurodegenerative diseases. Ideally, imaging techniques could predict cognitive decline, track disease progression and evaluate response to treatment. Moreover, as LB dementia is a neurodegenerative process, treatments that influence neuronal transmission, such as dopaminergic or cholinergic drugs, are not effective indefinitely. Thus, development of disease-modifying strategies, including interventions that target α -synuclein deposition, are of utmost importance.

References

- 1 Parkinson J: An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci* 2002; 14:223–236.
- 2 Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB: Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc* 2004;52: 784–788.
- 3 Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG: Cognitive impairments and depression in Parkinson's disease: a follow up study. *J Neurol Neurosurg Psychiatry* 1990;53:597–602.
- 4 Aarsland D, Larsen JP, Tandberg E, Laake K: Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc* 2000;48: 938–942.
- 5 Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E: Mental symptoms in Parkinson's disease are important contributors to caregiver distress. *Int J Geriatr Psychiatry* 1999;14:866–874.
- 6 Siderowf A, Ravina B, Glick HA: Preference-based quality-of-life in patients with Parkinson's disease. *Neurology* 2002;59:103–108.
- 7 Louis ED, Marder K, Cote L, Tang M, Mayeux R: Mortality from Parkinson disease. *Arch Neurol* 1997;54:260–264.
- 8 Aarsland D, Ballard CG, Halliday G: Are Parkinson's disease with dementia and dementia with Lewy bodies the same entity? *J Geriatr Psychiatry Neurol* 2004;17:137–145.
- 9 Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al: DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. *Neurology* 2007;68:812–819.

- 10 McKeith IG: Spectrum of Parkinson's disease, Parkinson's dementia, and Lewy body dementia. *Neurol Clin* 2000;18:865–902.
- 11 McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology* 2005;65:1863–1872.
- 12 Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald WI, Murphy D, et al: Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord* 2007;19:1061–1068.
- 13 Aarsland D, Litvan I, Salmon D, Galasko D, Wentzel-Larsen T, Larsen JP: Performance on the dementia rating scale in Parkinson's disease with dementia and dementia with Lewy bodies: comparison with progressive supranuclear palsy and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003;74:1215–1220.
- 14 Ballard CG, Aarsland D, McKeith I, O'Brien J, Gray A, Cormack F, et al: Fluctuations in attention: PD dementia versus DLB with parkinsonism. *Neurology* 2002;59:1714–1720.
- 15 Serrano C, Garcia-Borreguero D: Fluctuations in cognition and alertness in Parkinson's disease and dementia. *Neurology* 2004;63:S31–S34.
- 16 Horimoto Y, Matsumoto M, Nakazawa H, Yuasa H, Morishita M, Akatsu H, et al: Cognitive conditions of pathologically confirmed dementia with Lewy bodies and Parkinson's disease with dementia. *J Neurol Sci* 2003;216:105–108.
- 17 Barbas NR: Cognitive, affective, and psychiatric features of Parkinson's disease. *Clin Geriatr Med* 2006;22:773–796.
- 18 Cummings JL: The dementias of Parkinson's disease: prevalence, characteristics, neurobiology, and comparison with dementia of the Alzheimer type. *Eur Neurol* 1988;28(suppl 1):15–23.
- 19 Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P: Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. *Arch Neurol* 2003;60:387–392.
- 20 Chan SS, Chiu HF, Lam LC, Leung VP: Prevalence of dementia with Lewy bodies in an inpatient psychogeriatric population in Hong Kong Chinese. *Int J Geriatr Psychiatry* 2002;17:847–850.
- 21 Perry RH, Irving D, Tomlinson BE: Lewy body prevalence in the aging brain: relationship to neuropsychiatric disorders, Alzheimer-type pathology and catecholaminergic nuclei. *J Neurol Sci* 1990;100:223–233.
- 22 Shergill S, Mullan E, D'Ath P, Katona C: What is the clinical prevalence of Lewy body dementia? *Int J Geriatr Psychiatry* 1994;9:907–912.
- 23 Heidebrink JL: Is dementia with Lewy bodies the second most common cause of dementia? *J Geriatr Psychiatry Neurol* 2002;15:182–187.
- 24 Muslimovic D, Post B, Speelman JD, Schmand B: Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* 2005;65:1239–1245.
- 25 Foltynie T, Brayne CE, Robbins TW, Barker RA: The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. *Brain* 2004;127:550–560.
- 26 Hughes TA, Ross HF, Musa S, Bhattacharjee S, Nathan RN, Mindham RH, et al: A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology* 2000;54:1596–1602.
- 27 Williams LN, Seignourel P, Crucian GP, Okun MS, Rodriguez RL, Skidmore FM, et al: Laterality, region, and type of motor dysfunction correlate with cognitive impairment in Parkinson's disease. *Mov Disord* 2007;22:141–145.
- 28 Hughes TA, Ross HF, Musa S, Bhattacharjee S, Nathan RN, Mindham RHS, et al: A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology* 2000;54:1596–1602.
- 29 Levy G, Schupf N, Tang MX, Cote LJ, Louis ED, Mejia H, et al: Combined effect of age and severity on the risk of dementia in Parkinson's disease. *Ann Neurol* 2002;51:722–729.
- 30 Inzelberg R, Chapman J, Treves TA, Asherov A, Kiperavasser S, Hilkewicz O, et al: Apolipoprotein E4 in Parkinson disease and dementia: new data and meta-analysis of published studies. *Alzheimer Dis Assoc Disord* 1998;12:45–48.
- 31 Stern Y, Marder K, Tang MX, Mayeux R: Antecedent clinical features associated with dementia in Parkinson's disease. *Neurology* 1993;43:1690–1692.
- 32 Zgaljardic DJ, Foldi NS, Borod JC: Cognitive and behavioral dysfunction in Parkinson's disease: neurochemical and clinicopathological contributions. *J Neural Transm* 2004;111:1287–1301.
- 33 Hurig H, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, et al: Alpha-synuclein cortical Lewy bodies correlate with dementia in Parkinson's disease. *Neurology* 2000;54:1916–1921.
- 34 Vingerhoets G, Verleden S, Santens P, Miatton M, De Reuck J: Predictors of cognitive impairment in advanced Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;74:793–796.
- 35 Mosimann UP, Mather G, Wesnes KA, O'Brien JT, Burn DJ, McKeith IG: Visual perception in Parkinson disease dementia and dementia with Lewy bodies. *Neurology* 2004;63:2091–2096.
- 36 Lee C, Grossman M, Morris J, Stern MB, Hurtig HI: Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. *Brain Lang* 2003;85:347–356.
- 37 Grossman M, Kalmanson J, Bernhardt N, Morris J, Stern MB, Hurtig HI: Cognitive resource limitations during sentence comprehension in Parkinson's disease. *Brain Lang* 2000;73:1–16.
- 38 Weintraub D, Moberg PJ, Culbertson WC, Duda JE, Katz IR, Stern MB: Dimensions of executive function in Parkinson's disease. *Dement Geriatr Cogn Disord* 2005;20:140–144.
- 39 Uekermann J, Daum I, Peters S, Wiebel B, Przuntek H, Muller T: Depressed mood and executive dysfunction in early Parkinson's disease. *Acta Neurol Scand* 2003;107:341–348.
- 40 Tiraboschi P, Salmon DP, Hansen LA, Hofstetter RC, Thal LJ, Corey-Bloom J: What best differentiates Lewy body from Alzheimer's disease in early-stage dementia? *Brain* 2006;129:729–735.
- 41 Polymeropoulos MH, Lavedan C, Leroy E, et al: Mutation in the α -synuclein gene identified in families with Parkinson's disease. *Science* 1997;276:2045–2047.
- 42 Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E: Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.
- 43 Colosimo C, Hughes AJ, Kilford L, Lees AJ: Lewy body cortical involvement may not always predict dementia in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003;74:852–856.
- 44 Ballard C, Ziabreva I, Perry R, Larsen JP, O'Brien J, McKeith I, et al: Differences in neuropathologic characteristics across the Lewy body dementia spectrum. *Neurology* 2006;67:1931–1934.
- 45 Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW: Parkinson disease neuropathology: later-developing dementia and loss of the levodopa response. *Arch Neurol* 2002;59:102–112.
- 46 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.
- 47 Savitt JM, Dawson VL, Dawson TM: Diagnosis and treatment of Parkinson disease: molecules to medicine. *J Clin Invest* 2006;116:1744–1754.
- 48 Pandey UB, Nie Z, Batlevi Y, McCray BA, Ritson GP, Nedelsky NB, et al: HDAC6 rescues neurodegeneration and provides an essential link between autophagy and the UPS. *Nature* 2007;447:859–863.
- 49 Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM: Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci* 2003;23:6351–6356.
- 50 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.

- 51 Shaw LM, Korecka M, Clark CM, Lee VM, Trojanowski JQ: Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Rev Drug Discov* 2007;6:295–303.
- 52 Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, et al: Ubiquitination of a new form of α -synuclein by parkin from human brain: implications for Parkinson's disease. *Science* 2001;293:263–269.
- 53 Scherzer CR, Eklund AC, Morse LJ, Liao Z, Locascio JJ, Fefer D, et al: Molecular markers of early Parkinson's disease based on gene expression in blood. *Proc Natl Acad Sci USA* 2007;104:955–960.
- 54 Brooks DJ: PET and SPECT studies in Parkinson's disease. *Baillieres Clin Neurol* 1997; 6:69–87.
- 55 Jennings DL, Seibyl JP, Oakes D, Eberly S, Murphy J, Marek K: (123I) β -CIT and single-photon emission computed tomographic imaging versus clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. *Arch Neurol* 2004;61:1224–1229.
- 56 Walker Z, Costa DC, Walker RW, Lee L, Livingston G, Jaros E, et al: Striatal dopamine transporter in dementia with Lewy bodies and Parkinson disease: a comparison. *Neurology* 2004;62:1568–1572.
- 57 Hilker R, Thomas AV, Klein JC, Weisenbach S, Kalbe E, Burghaus L, et al: Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. *Neurology* 2005;65:1716–1722.
- 58 Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, et al: Imaging β -amyloid burden in aging and dementia. *Neurology* 2007; 68:1718–1725.
- 59 Siderowf A, Newberg AB, Chou KL, Lloyd M, Colcher A, Hurtig H, et al: [99m Tc]TRO-DAT-1 SPECT imaging correlates with odor identification in early Parkinson disease. *Neurology* 2005;64:1716–1720.
- 60 Hawkes C: Olfaction in neurodegenerative disorder. *Mov Disord* 2003;18:364–372.
- 61 Burn DJ, McKeith IG: Current treatment of dementia with Lewy bodies and dementia associated with Parkinson's disease. *Mov Disord* 2003;18(suppl 6):S72–S79.
- 62 Weintraub D, Siderowf AD, Potenza MN, Goveas J, Morales KH, Duda JE, et al: Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Arch Neurol* 2006;63:969–973.
- 63 Molloy SA, Rowan EN, O'Brien JT, McKeith IG, Wesnes K, Burn DJ: Effect of levodopa on cognitive function in Parkinson's disease with and without dementia and dementia with Lewy bodies. *J Neurol Neurosurg Psychiatry* 2006;77:1323–1328.
- 64 Contarino MF, Daniele A, Sibilio AH, Romito LM, Bentivoglio AR, Gainotti G, et al: Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:248–252.
- 65 Lippa CF, Smith TW, Perry E: Dementia with Lewy bodies: choline acetyltransferase parallels nucleus basalis pathology. *J Neural Transm* 1999;106:525–535.
- 66 Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham CA, et al: Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1985;48:413–421.
- 67 Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, Crawley A, et al: Donepezil for dementia in Parkinson's disease: a randomised, double blind, placebo controlled, crossover study. *J Neurol Neurosurg Psychiatry* 2005; 76:934–939.
- 68 Miyasaki JM, Shannon K, Voon V, Ravina B, Kleiner-Fisman G, Anderson K, et al: Practice Parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:996–1002.
- 69 Aarsland D, Mosimann UP, McKeith IG: Role of cholinesterase inhibitors in Parkinson's disease and dementia with Lewy bodies. *J Geriatr Psychiatry Neurol* 2004;17:164–171.
- 70 McKeith I, del Ser T, Spano P, Emre M, Wesnes K, Anand R, et al: Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 2000;356: 2031–2036.
- 71 Richard IH, Justus AW, Greig NH, Marshall F, Kurlan R: Worsening of motor function and mood in a patient with Parkinson's disease after pharmacologic challenge with oral rivastigmine. *Clin Neuropharmacol* 2002; 25:296–299.
- 72 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.
- 73 Rabey JM, Prokhorov T, Miniovitz 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.