Parkinson’s Disease and Dementia
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Parkinson’s disease affects as many as 1 million Americans and with advanced age is complicated by dementia in a majority of cases. However, the recognition of cognitive impairment in Parkinson’s disease is made complicated by the predominance of motor symptoms and a neuropsychiatric profile that differs from the more common dementia of the Alzheimer’s type. Differentiating the decline in personal and social activities due to cognitive impairment rather than preexisting movement disorder is difficult. Several expert bodies have addressed the use of cholinesterase inhibitors for the dementia of Parkinson’s disease, but the evidence base is far less substantial than that which exists for Alzheimer’s disease. Although most patients with Parkinson’s disease dementia should be offered a trial of anti-cholinesterase therapy, particularly those experiencing hallucinations, dramatic benefits are not common. Temporary symptomatic relief rather than disease modification is the most that can be expected. As a result, treatment should be presented as an option rather than an imperative.

INTRODUCTION

Parkinson’s disease has a mean age of onset of 57 years and a prevalence of 1% to 2% among adults ≥60 years of age. There may be as many as 1 million Americans with the illness. It is manifested by bradykinesia, rigidity, resting tremor, postural instability, frozen gait disorder, and flexed posture. The progression and severity of Parkinson’s disease varies widely and the associated motor disability may be substantially reduced by numerous medications singly or in combination. The goal is an increase in brain dopamine through either enhanced production or reduced breakdown of the molecule. The disease begins as a movement disorder, but with advancing age is complicated by dementia in as many as 80% of patients. The characteristic frozen facial expression, slowed cognition (bradyphrenia), fluctuation in attention, and motor impairment compounded by depression and hallucinations make the assessment of possible dementia challenging. In addition, dopaminergic medications precipitate hallucinations with recognized frequency. Although medication to treat the dementia of Parkinson’s disease is most often modestly effective for patients in aggregate, failure to recognize dementia means that the minority of individuals who might receive substantial benefit will not be offered a therapeutic trial. As a result, practitioners need guidance to efficiently assess cognitive decline among people with Parkinson’s disease as well as realistic expectations for the benefits of dementia treatment.

SIMILARITIES AND DIFFERENCES WITH OTHER DEMENTIAS

Loss of dopaminergic neurons in the substantia nigra is the hallmark of Parkinson’s disease and the basis for the use...
of dopamine agonists. In contrast, neuronal dropout in the entorhinal cortex and hippocampus are seen in Alzheimer’s disease. Yet, similar to Alzheimer’s disease, cholinergic deficits are common in Parkinson’s disease and parallel the decline in cognition. Hematoxilin and eosin staining neuronal inclusions known as Lewy bodies occur in both Parkinson’s and Lewy body dementia but not in Alzheimer’s disease. However, amyloid plaques and neurofibrillary tangles thought to be the signature pathology of Alzheimer’s disease commonly occur in both Parkinson’s disease and Lewy body dementia as well, though less extensively. Differences between Alzheimer’s disease and the dementia of Parkinson’s and Lewy body disease detected by imaging studies, whether structural (magnetic resonance imaging [MRI], computerized axial tomography) or metabolic (positron emission tomography, single photon emission computed tomography, functional MRI), are too subtle for use in clinical diagnosis.

Clinical features of Alzheimer’s, Parkinson’s, and Lewy body dementia overlap as severity progresses but significant differences are apparent in the early stages (Table 1). In Alzheimer’s disease, memory impairment is prominent with executive dysfunction, aphasia, apraxia, and anoma often present but less obvious. In Parkinson’s disease, hallucinations occur in 10% of cases most often at the mid- to later stage of the disease. Severe motor impairments in gait, balance, muscle strength, and swallowing occur in the later stages. In Parkinson’s dementia, the movement disorder precedes the onset of cognitive impairment. Inattention, executive dysfunction, bradyphrenia, and visuospatial deficits may be more noticeable than impaired memory. Hallucinations are four times more frequent and visuospatial deficits may be more prominent in Alzheimer’s disease. More severe postural instability and gait disorder predict the onset of dementia among people with Parkinson’s disease. Incident hallucinations also predict the subsequent emergence of dementia.

Hallucinations are also a distinguishing feature of Lewy body dementia. Marked fluctuations in attentiveness and mild impairment in memory—both of which precede the appearance of rigidity, tremor, postural instability and gait disorder—distinguish Lewy body dementia from that of Parkinson’s disease. Unanticipated sensitivity to neuroleptic-induced extrapyramidal symptoms also indicates that Lewy body dementia, rather than Alzheimer’s disease with hallucinations, is the correct diagnosis.

EFFICIENT SCREENING PROCEDURES

Not every older adult should be screened for cognitive impairment. Screening in clinical practice is predicated on the recognition of cognitive decline interfering with personal or social activities by the patient, family, or clinician. However, Parkinson’s disease often impacts social and personal activities as a result of motor impairment. Thus, personal responsibilities may already have been abandoned before impaired cognition could have made noticeable contribution. Given the elevated frequency with which dementia emerges in Parkinson’s disease, the practitioner’s concern for impairment should be heightened. When hallucinations, apathy, or excessive daytime drowsiness appear after a period of stable treatment, dementia should be suspected.

In a 2007 review on the diagnosis and treatment of Parkinson’s disease dementia, the Movement Disorders Society’s taskforce recommended the Mini-Mental State Examination (MMSE) as a global measure of cognitive performance in which a score <26 indicates impairment. They also suggested a number of screening procedures to detect impairments in specific cognitive domains. These included domains of attention, visuo-constructional ability, executive function, and memory. Parkinson’s disease patients with impairments in more than one domain associated with deterioration in personal care or social activities would meet the criteria for dementia. Attention would be assessed with the serial seven subtraction task from the MMSE or by asking the patient to list months of the year in reverse order. In either test, two errors or omissions is considered evidence of impairment. For executive dysfunction, impairment is defined as failure to recite nine examples from the lexical category of words starting with the letter “S” in one minute or inability to draw a clock with the time set at 10 past 2. Visuo-constructional impairment is defined by inability to copy two intersecting pentagons from the MMSE. Impairment in memory is defined by failure to recall all three words from the MMSE’s registration and recall task. The review also provides a comprehensive listing of neuropsychological instruments that have been used to assess cognition among people with Parkinson’s disease.

However, busy practitioners may find the copyrighted MMSE and clock drawing cumbersome. As an alternative, the Memory Impairment Screen and the oral version of the Trail Making Test for executive function do not require paper and pencil, may be administered by phone, and are quite brief. Both have been validated as screening measures for use in population assessments of dementia. For the Memory Impairment Screen, the subject is tasked to repeat and remember four words (eg, apple, table, penny, spoon).
given in sequence at 1-second intervals and then asked to recall each when prompted with a category cue (eg, fruit, furniture, money, utensil). The registration phase may be repeated up to five times before moving to the next test. Next, the subject is asked to recite the alphabet from “A to Z” and then to count from 1–25. The person is then asked to continue the sequence, which the examiner starts with “One A, Two B, Three C, Four ?” Subjects making two errors as they reach “M 13” are considered to exhibit executive impairment. Following the Trail Making test, the examiner returns to the Memory Impairment Screen by asking the subject to recall the four words that were previously rehearsed. Allowing 1 minute for free recall the examiner then provides the category cue for each word not remembered spontaneously. Words recalled freely receive a score of 2; those that required the cue for recall receive a score of 1. A total score of 4 is predictive of dementia.

### TABLE 1

**DIAGNOSTIC CRITERIA FOR ALZHEIMER’S DISEASE, PARKINSON’S DISEASE DEMENTIA, AND DEMENTIA WITH LEWY BODIES**

Diagnostic features shared by Alzheimer’s, Parkinson’s and Lewy body dementia include 1) a decline in cognitive performance which interferes with the person’s occupational, personal or social activities, 2) the finding that reversible causes of the decline such as infection or delirium have been ruled out, 3) memory impairment need not be prominent initially but should become more so as the dementia progresses, 4) distinguishing features should not be associated with more than minimal evidence of cerebrovascular disease evident on brain imaging.

<table>
<thead>
<tr>
<th><strong>Alzheimer’s Disease</strong></th>
<th><strong>Parkinson’s Disease Dementia</strong></th>
<th><strong>Dementia with Lewy Bodies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement disorder or focal neurologic findings absent until late in the course of illness</td>
<td>Movement disorder precedes cognitive decline</td>
<td>Occurs before or concurrently with Parkinson’s disease; mental impairment is more prominent than the movement disorder</td>
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<tr>
<td><strong>Insidious onset of impairment in learning and recall plus one or more of the following:</strong></td>
<td><strong>Core features</strong></td>
<td><strong>Core features</strong></td>
</tr>
<tr>
<td>1. Aphasia (difficulty with communication, understanding)</td>
<td>1. Occurs in the context of well-established Parkinson’s disease</td>
<td>1. Pronounced fluctuation in attention and alertness</td>
</tr>
<tr>
<td>2. Apraxia (difficulty manipulating objects in space)</td>
<td>2. Insidious onset</td>
<td>2. Recurrent, vivid hallucinations</td>
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<tr>
<td>3. Agnosia (faulty object recognition)</td>
<td>3. Impairment in more than one cognitive domain</td>
<td>3. Spontaneous features of parkinsonism</td>
</tr>
<tr>
<td>4. Executive dysfunction (impaired capacity to plan, remain focused on the task)</td>
<td><strong>Associated features</strong></td>
<td><strong>Suggestive features</strong></td>
</tr>
<tr>
<td></td>
<td>1. Impaired, fluctuating attention</td>
<td>1. REM sleep behavior disorder</td>
</tr>
<tr>
<td></td>
<td>2. Executive dysfunction</td>
<td>2. Marked neuroleptic sensitivity</td>
</tr>
<tr>
<td></td>
<td>3. Impairments in visuo-spatial function</td>
<td><strong>Supportive features</strong></td>
</tr>
<tr>
<td></td>
<td>4. Memory impairment (recognition and cued recall better than free recall)</td>
<td>1. Falls</td>
</tr>
<tr>
<td></td>
<td>5. Language (word finding difficulties)</td>
<td>2. Transient unexplained syncope, loss of awareness</td>
</tr>
<tr>
<td></td>
<td>6. Apathy, inertia</td>
<td>3. Severe autonomic dysfunction (orthostatic hypotension)</td>
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<tr>
<td></td>
<td>7. Personality change (anxious, depressed)</td>
<td></td>
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<tr>
<td></td>
<td>8. Vivid hallucinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. Delusions of persecution or phantom intruders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10. Excessive daytime drowsiness</td>
<td></td>
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</tbody>
</table>

REM=rapid eye movement.

A free demonstration of the Trail Making Test, clock-drawing test, and other measures of executive dysfunction can be accessed on the Internet. Baseline assessment of cognition with simple screening procedures following the diagnosis of Parkinson’s disease will set the stage for detection of genuine impairment should warning signs of dementia emerge.

RESPONSIVENESS TO CHolinESTerase INHIBITORS

The evidence base regarding the efficacy of pharmacotherapy for Parkinson’s disease dementia is limited but more extensive if one considers the illness to be part of a spectrum including dementia with Lewy bodies. In the largest randomized controlled trial to date, Emre and colleagues conducted a pivotal study of 541 people whose Parkinson's disease was accompanied by mild-to-moderate dementia defined by MMSE score of 10–24. Patients were allocated to rivastigmine or placebo in a 2:1 ratio. Rivastigmine 1.5 mg was introduced and titrated to a maximum tolerated dose or 12 mg over 16 weeks. Exclusion criteria included a history of major depressive disorder, use of cholinesterase inhibitor or anticholinergic drug, or change in Parkinson's disease medication within 4 weeks of enrollment. The initiation of a psychotropic medication during the study with the exception of an antipsychotic for an acute episode of psychosis was forbidden. The mean age of study participants was slightly >72 years and 66% were men. Forty percent were diagnosed with a mental disorder in addition to dementia.

Greater than 25% of participants were taking an antipsychotic at baseline, 25% were on an antidepressant, 20% were on a benzodiazepine or sedative hypnotic, and 95% were taking levodopa. The two primary efficacy measures were the Alzheimer’s Disease Assessment Scale (ADAS-cog) and the Alzheimer’s Disease Cooperative Study-Clinician’s Global Impression of Change (ADCS-CGIC). Each were separately assessed by trained raters blind to the assessment outcome. The ADAS-cog is a 70-point measure of cognitive performance. The ADCS-CGIC is a 7-point categorical scale anchored at baseline where “1” equals marked improvement, “7” equals marked worsening, and “4” denotes no change. Detectable changes that were not clinically meaningful were defined as minimal; changes associated with obvious clinical improvement were defined as moderate. Secondary efficacy measures included the ADCS measure of activities of daily living, the Neuropsychiatric Inventory, the MMSE, tests of attention and reaction time, and tests of executive function as measured by letter-category verbal fluency and clock-drawing.

At the end of dose titration, >50% of treated participants were taking rivastigmine 9–12 mg/day. Of those completing the study, 72% were in the rivastigmine group and 82% in placebo. Adverse events accounted for most of the premature withdrawals in both groups. Nausea (29%), vomiting (16.6%), and worsening tremor (10.2%) were significantly more frequent among the rivastigmine group. Of the efficacy measures comparing rivastigmine to placebo, at 24 weeks all were statistically significant. There was an 11.7% difference in cognitive performance (ADAS-cog) between drug and placebo groups. Clinically meaningful (marked to moderate) improvement was seen in 14.5% of placebo and 19.8% of the rivastigmine group. Clinically meaningful deterioration was seen in 23.1% of placebo and 13.0% of the rivastigmine group. Among the secondary measures of disability, neuropsychiatric symptoms, cognition, and executive functions all showed improvement with rivastigmine and decline with placebo with the differences being statistically significant.

Emre and colleagues conclude that their findings among patients with Parkinson’s disease and dementia are similar to those seen in studies of cholinesterase inhibitors for Alzheimer’s disease. A free demonstration of the Trail Making Test, clock-drawing test, and other measures of executive dysfunction can be accessed on the Internet. Baseline assessment of cognition with simple screening procedures following the diagnosis of Parkinson’s disease will set the stage for detection of genuine impairment should warning signs of dementia emerge.

### TABLE 2

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Dose</th>
<th>Final Dose</th>
<th>Precautions</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivastigmine</td>
<td>Exelon patch</td>
<td>4.6 mg</td>
<td>9.5 mg</td>
<td>Transient, initial nausea vomiting; titrated up at week 4; abrupt withdrawal leads to abrupt decline; patch must be rotated to different areas</td>
<td>Transdermal patch applied once daily; FDA approved for Parkinson's dementia</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Aricept</td>
<td>5 mg</td>
<td>10 mg</td>
<td>Transient, initial nausea vomiting; titrated up at week 4; abrupt withdrawal leads to abrupt decline</td>
<td>Oral dose taken QD</td>
</tr>
</tbody>
</table>

FDA=Food and Drug Administration.

disease. Benefits are modest, representing a 6-month reprieve in the course of symptoms without genuine disease modification. However, close to one in five patients will show dramatic benefit obvious to the family and the clinician alike. Indeed, Press advocates the family’s impression of benefit over formal neuropsychological measures to assess the effectiveness of treatment. Given that benefits if apparent at all emerge within the first weeks of treatment, the most realistic expectation for patient and family is a 60–90-day trial of therapy rather than an open-ended course. Also noteworthy were the relatively more substantial benefits of rivastigmine for neuropsychiatric symptoms, including hallucinations, a finding similar to McKeith and colleagues' rivastigmine study of 120 patients with Lewy body dementia. The number of study participants receiving a neuroleptic during the Emre and colleagues study was considered low. Low doses of atypical antipsychotics such as olanzapine, quetiapine, and clozapine were initially used to control levodopa-induced hallucinations because they were less likely than typical antipsychotics to induce extrapyramidal symptoms.

However, the 2005 Food and Drug Administration warning of increased mortality when prescribed to patients with dementia amplified by more recent reports raise the threshold at which these agents may be considered for psychosis in dementia nearly out of reach. Clearly, a trial of cholinesterase therapy should be recommended to reduce hallucinations of dementia in Parkinson’s disease before a neuroleptic is offered. The transdermal rivastigmine patch with less frequent gastrointestinal effects, not available at the time of Emre’s study, is an added advantage. It should be added that other cholinesterase inhibitors may be efficacious for the dementia of Parkinson’s disease but have not been subjected to large-scale trials. Nonetheless, the Cochrane Review and other sources find at least minimal evidence to support the use of donepezil as well (Table 2).

**CONCLUSION**

Dementia is such a frequent complication that every older patient with Parkinson’s disease should be screened for memory impairment and executive dysfunction, particularly if hallucinations emerge in the context of stable dopaminergic treatment. The impact of cholinesterase inhibitor therapy on cognition and activities of daily living will be obvious in only one patient in five. However, the reduction in hallucinations may be more robust. Consistent reports of elevated mortality associated with antipsychotics prescribed to people with dementia make cholinesterase inhibitor therapy preferable when hallucinations emerge. A 60–90-day trial of a cholinesterase inhibitor should be adequate to give the patient, family, and practitioner sufficient evidence on which to base a decision for ongoing treatment. In equivocal cases, the medication can be reintroduced if visible decline is observed following discontinuation. With adverse reactions and lack of efficacy taken into account, 40% to 60% of treated patients will withdraw from cholinesterase inhibitor therapy. However, lacking predictors of treatment responsiveness and balancing in the safety of cholinesterase inhibitor therapy, most patients with Parkinson’s disease dementia should be offered a trial of treatment. Practitioners’ zeal for treatment must be tempered by the realization that temporary symptomatic relief rather than disease modification is the most that can be expected. As a result, treatment should be presented as an option rather than an imperative.

**REFERENCES**

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