Mild cognitive impairment in Parkinson's disease: the challenge and the promise

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Abstract: This review addresses the literature surrounding Parkinson's disease (PD) and mild cognitive impairment (MCI). It discusses the neuropsychological, pharmaceutical, and pathological overlap, the socioeconomic impact of PD and MCI, and the value of recognizing, understanding, and treating MCI in PD. It is concluded from this review that MCI in PD does exist and should be considered in clinical and research investigations. Due to the lack of accepted clinical criteria, an inclusive operating definition of MCI in PD is proposed. Research guidelines for studying the presence of MCI in PD and evaluating the efficacy of pharmaceutical interventions are also suggested.

Keywords: Parkinson's, dementia, mild cognitive impairment, therapy, cognition

Introduction

Dementia in Parkinson's disease (PD) and, in particular, mild cognitive impairment (MCI) has been difficult to define. Dementia is generally considered an acquired and persistent deterioration of the intellect in an alert person. What differentiates dementia from other cognitive impairments, such as MCI, is that in dementia, cognitive impairment results in a significant interference with work or usual social activities (APA 2000). The latest DSM version defines dementia as "the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning" (APA 2000, p 148). Dementia is, thus, largely a clinical diagnosis corroborated by psychometric testing.

The 4 cognitive domains that can be affected include: (1) *recent memory* – the ability to learn, retain, and retrieve newly acquired information; (2) *language* – the ability to comprehend and express verbal information; (3) *visual spatial function* – the ability to manipulate and synthesize non-verbal, geographic, or graphic information; and (4) *executive function* – the ability to perform abstract reasoning, solve problems, plan for future events, mentally manipulate more than one idea at a time, maintain mental focus in the face of distraction, or shift mental effort easily.

This article discusses the different types of dementia, their socioeconomic impact and how they relate to Parkinson's disease (PD); provides an overview of MCI, its definition and subtypes; describes the current challenges in understanding MCI in PD; and discusses the value of recognizing, understanding, and treating MCI in PD.

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Incidence and prevalence of dementia in Parkinson's disease

The definition and frequency of dementia in PD is controversial. Incidence rates for PD dementia range from 4.2%–9.5% per year (Hughes et al 2000; Aarsland, Anderson,

et al 2001). Depending on the sample population and criteria used, the prevalence rate of PD dementia ranges from 10%–40%. If the higher prevalence rates are correct, PD could be the second most common cause of dementia after Alzheimer's disease (AD).

One epidemiologic study estimates that 65%–70% of demented individuals suffer from AD; 13%–15% have dementia with Lewy bodies (DLB); 8%–10% have PD; and 5%–10% are due to vascular dementia. However, other epidemiologic studies do not include PD as a major source of dementia in the elderly (Meyer et al 1988; Pillon et al 1991; Wahlund et al 2003).

In a population-based study of PD with and without dementia, the crude PD prevalence was 99.4/100 000 and the crude PD dementia prevalence was 41.1/100 000. The prevalence of dementia increased with age, from 0 (for < 50 years of age) to 787.1/100 000 (for > 79 years of age). Interestingly, in that study, the major difference between PD patients with and without dementia was a later onset of motor manifestations in demented PD (Mayeux et al 1992).

By 2050, it is projected that the number of individuals over 65 will increase to 1.1 billion worldwide. As a consequence, the number of dementia cases may reach 37 million. By 2050, the total cost of dementia as an illness is estimated to reach US$383 billion in the USA (Lockhart and Lestage 2003).

More importantly, dementia seems to decrease survival rates. The median survival of a person with dementia from onset to death is about 6 years. A treatment capable of delaying the onset of AD, for example, by 5 years (ie, 50% risk reduction), reduces the prevalence rate of AD by 4.04 million by the year 2050. Delaying the onset by only 6 months reduces the number of demented patients by 380 000. From the medicoeconomic standpoint, this 6-month delay in the onset of dementia is estimated to result in average annual savings of US$18 billion by 2050.

Mild cognitive impairment

MCI is in an intermediate zone between normal cognition and dementia. Clinicians view MCI differently. It is seen as either a "disease" representative of a homogenous population of individuals in an early prodromal stage of clinically defined AD, or a heterogeneous "syndrome" representing an early or transitional stage of different forms of dementia. Through the years, various terms have been used to describe the MCI state, such as, cognitively impaired not demented, possible dementia syndrome, age-associated memory impairment, and age-associated cognitive impairment.

Table 1 Heterogeneity of mild cognitive impairment in various dementing states

Type of MCI	May progress to:
Amnestic MCI	Alzheimer's disease
Multiple domains, mild impairment	Alzheimer's disease Vascular dementia Dementia with Lewy bodies Normal aging
Single non-memory domain	Frontotemporal demetia Primary progressive aphasia Dementia with Lewy bodies Vascular dementia

Abbreviation: MCI, mild cognitive impairment.

There are several subtypes of MCI that are believed to represent prodromal stages for several dementing illnesses (see Table 1). MCI can predominantly affect a single cognitive memory (or non-memory) domain, or affect multiple cognitive domains. The most well described and studied of the MCI subtypes is the "amnestic" form. Its working criteria are listed in Table 2. In amnestic MCI, memory is affected to a significant degree (approximately 1.5 SD below age- and education-matched normal subjects), while other domains might be very mildly impaired at perhaps less than 0.5 SD below appropriate comparison subjects (Petersen et al 1999). In multiple domain MCI, several cognitive domains are impaired at perhaps the 0.5–1.0 SD level of impairment. Subjects may have slight memory impairment in conjunction with mild impairment in, eg, executive function and language. The distinction between multiple domain MCI and amnestic MCI is that no single domain is impaired out of proportion to the other cognitive domains. Finally, a third clinical variety of MCI could involve a mild impairment in a single non-memory cognitive domain. This form of MCI, known as single non-memory-domain MCI, is characterized by a person having a relatively isolated impairment in a single non-memory domain such as executive function, visuospatial processing, or language.

Table 2 Amnestic mild cognitive impairment working criteria

1. Memory complaint, preferably corroborated by an informant
2. Objective memory impairment for age and education
3. Largely intact general cognitive function
4. Essentially preserved activities of daily living
5. Not demented

Despite the guidelines listed above, the diagnosis of MCI remains challenging. The standard deviation cut-offs used for single domain (eg, –1.5 SD) or multiple domain (eg, –0.5 to –1.0 SD) cannot be generalized to all patients. This is because a patient's premorbid level of functioning may influence his/her performance on neuropsychological measures (ie, measures of memory, attention, etc). For this reason, researchers should also incorporate findings from a clinical interview and a standardized assessment of premorbid intellectual functioning (ie, traditional "hold" domains of cognitive functioning) for diagnostic purposes. These additional procedures are necessary when test norms do not include correction scores for education level. Other considerations for reducing diagnostic false positives include using a more stringent cut-off score of –2.0 SD (where less than 2% of the population score). Interestingly, however, researchers tend not to use this stringent cut-off score out of concern that they will fail to classify patients' milder forms of cognitive impairment. Consequently, despite literature recommendations, there remains a fine balance between the statistical and practical issues of use of cut-off scores for MCI diagnostic purposes.

All subtypes of MCI are distinguishable from full dementia. The cognitive impairment in MCI, although objectively seen and subjectively noticed, is not severe enough to sufficiently impair activities of daily living and normal social functioning. Since MCI does not significantly affect general day-to-day function, its definition should therefore involve a combination of both clinical skill and neuropsychological test findings.

The challenge

The incidence of dementia and MCI in PD remains unclear

Due to the lack of a universal set of criteria to identify cognitive impairment in PD, the reported prevalence of dementia in PD ranges from 10%–95% (Marttila and Rinne 1976; Lieberman et al 1979; Boller et al 1980; Brown and Marsden 1984; Mayeux et al 1988, 1992; Yoshimura 1988; Friedman and Barcikowska 1994; Aarsland et al 1996).

One prospective study conducted over 3.5 years, involving 140 non-demented PD and 572 controls, showed 19.2% of PD patients became demented within 2 years compared with 15.2% of controls. Parkinson patients were almost two times more likely to develop dementia compared with controls (RR = 1.7; CI: 1.1–2.7). Predictive features for dementia included a Unified Parkinson's Disease Rating Scale (UDPRS) score > 25 (ie, more severe motor impairment) and the presence of depression (Marder et al 1995).

Even the rate of progression of the most well defined MCI subtype (ie, amnestic MCI) to AD has not been homogenous. The conversion rate ranges from 0% to 21% at one year, 6%–33% between two and three years, and 37%–58% at five years. Remarkably, there are a relatively high percentage of individuals who remain stable or revert from MCI diagnosis back to normal. A 5-year prospective study on MCI shows 39% converted to AD, 42 % remained stable, and 19% showed improvement in their neuropsychiatric profiles, leading the authors to state that the "large heterogeneity in the progression of suspected MCI make it a difficult diagnostic entity … This suggests that current psychometric criteria used to evaluate MCI are not sufficiently refined …" (Petersen et al 1999, p 304).

However, despite the heterogeneity, longitudinal follow-up studies show individuals with MCI consistently progress to clinically probable AD at a rate between 6%–15% per annum, and up to 70%–80% convert to full dementia within 10 years (Petersen et al 1999).

The etiology of dementia in PD is heterogeneous

Most single photon emission computerized tomography (SPECT) studies in PD show a heterogeneous regional cerebral blood flow (rCBF) pattern. Three main subtypes or patterns of hypoperfusion in PD with dementia are often described. One study shows 22% of PD patients with dementia exhibit frontal hypoperfusion, 64% have temporoparietal hypoperfusion (similar to that seen in AD), and 14% exhibit multiple focal deficits (similar to that seen in vascular dementia) (Yoshimura 1988).

Another functional imaging study comparing the PET scans of various dementing neurodegenerative illnesses shows a clearer, more homogenous pattern for conditions such as corticobasal ganglionic degeneration (CBGD) and progressive supranuclear palsy (PSP) compared with PD, DLB, or AD. CBGD patients uniformly exhibit asymmetric hypometabolism of cortex and thalamus. PSP patients have global reduction especially in the frontal lobe and basal ganglia, whereas positron emission tomography (PET) studies in AD, PD with dementia, and mild DLB all show a similar resting pattern of frontotemporoparietal hypometabolism. Ultimately this study led to the unsatisfactory conclusion that "metabolic PET can distinguish CBGD and

PSP but not PDD, AD or DLB" (Turjanski and Brooks 1997, p 37).

Although general rules are often followed, neuropsychological tests also show similar overlap, especially between DLB and demented PD patients. As an example, a study looking at the clinical and neuropsychological profiles of 16 patients with DLB, 15 PD patients with dementia, and 16 patients with AD found no difference in the performance of various cognitive tasks such as verbal memory, attention, visual perception, and construction. Clinically, PD and DLB patients do not differ in the UPDRS motor scores in this study (Noe et al 2004).

The pathology of these disorders does not aid in the differentiation of cognitive impairment. One autopsy study showed that up to 60% of clinically diagnosed PD patients had senile plaques and neurofibrillary tangles in the hippocampus or neocortex (Hakim and Mathieson 1978; Duyckaerts et al 1993). Thus, it may be likely that only a minority of demented PD patients have the classical "subcortical" PD dementia. The rest of PD patients may have superimposed AD-type dementia and/or dementia from vascular causes (PD commonly occurs in the elderly, where stroke risk factors are at their peak). Thus, the functional imaging, neuropsychiatric profile, and pathology support the heterogeneity of dementia in PD, and none of these definitely differentiates the exact cause of cognitive impairment. If the etiology of dementia in PD is, indeed, heterogeneous and overlapping with other forms of dementia, then its likely precursor, MCI in PD, is more likely to be heterogeneous as well.

Further complicating this already confusing picture is that DLB, a dementing illness strongly associated with parkinsonian features, is still not recognized by all experts as a separate disease entity from PD. There is increasing consensus that DLB may be a variant of PD dementia, and that both conditions may be the opposite ends of the spectrum of one illness. The 3rd International Workshop on DLB and PD dementia (Newcastle-upon-Tyne, UK; 2003 Sep 17–20) highlights the findings that the principal correlate of dementia in PD is the presence of Lewy bodies in the limbic and neocortex – similar to that of DLB. The amount of concomitant AD pathology in PD dementia is, however, typically less than that in classic DLB. The clinical features of PD dementia are similar to those of DLB, with attentional deficits, executive abnormalities, and frequent concomitant neuropsychiatric disturbances, including visual hallucinations and delusions. Participants from the 3rd International Workshop on DLB and PD Dementia supported abolishing the "1-year rule" that conveniently separates PD dementia from DLB. Patients whose disease begins with cognitive impairment will be diagnosed as having DLB. Illnesses beginning with a parkinsonian syndrome and meeting criteria for PD will be diagnosed with PD dementia when dementia occurs, regardless of the timing of its occurrence. This consensus, however, does not solve the fundamental question of true etiology and the significance of pathology to the clinical syndrome.

There is no uniform definition of MCI especially in Parkinson's disease

"How wide the net for MCI is cast will affect the prevalence and severity of its functional consequences" (Albert et al 2002, p 64). A 5-year prospective study of 1790 geriatric patients shows that the most commonly used case definition of amnestic MCI yields a population prevalence estimate of 1.03% (95% CI 0.66–1.40). Eliminating the requirements for subjective memory complaints and intact activities of daily living increases the prevalence to 3.02% (95% CI 2.4–3.64). However, the 5-year outcomes, including the risk of death, institutionalization, and conversion to full dementia, are not distinctly different among the various case definitions of MCI. Regardless of the MCI criteria used, most people with amnestic MCI develop dementia, chiefly AD, after 5 years (RR = 9.3–19.7). Thus, in this large study, variations in case definition affect prevalence but not outcomes of MCI (Fisk et al 2003).

Although it may seem premature to propose an operating criteria for MCI in PD, there are sufficient clinical, psychometric, radiological, and pathological findings on cognitive impairment in PD that help guide which principal concepts should be incorporated in the future definition of MCI. First, because MCI does not significantly affect activities of daily living, it is dangerous to have purely clinical MCI criteria. Its definition should be an equal combination of clinical and psychometric criteria. Second, the clinical criteria for "probable" idiopathic PD need to be strictly incorporated. Third, because of the heterogeneity of dementia in PD, the three main subtypes of MCI (amnestic, multiple domain, single-non-memory domain type), which could all lead to dementia in PD, should be included in the clinical and psychometric criteria.

Due to the lack of accepted criteria for MCI in PD, an inclusive operating definition is proposed below:

1. Meet the clinical criteria for "probable" idiopathic PD (eg, having at least 2 out of 3 features of parkinsonism:

resting tremor, bradykinesia, rigidity; with a sustained significant response to dopaminergic therapy).
2. Clinically:
   a. Memory complaint (forgetfulness) OR complaints in attention/executive function (slowed thinking, difficulty manipulating information, lack of concentration, etc) OR isolated complaints on other domains such as visuospatial processing or language; preferably corroborated by an informant.
   b. Essentially preserved activities of daily living.
   c. Not demented.
3. Psychometrically:
   a. Largely intact general cognitive function.
   b. With an objective impairment (that corresponds to the above subjective complaints) as measured psychometrically: ie, 1.0–1.5 SD below age- and education-matched normal subjects in one cognitive domain, such as memory or other single non-memory domain, while other domains are mildly affected at less than 0.5 SD below appropriate controls; OR 0.5–1.0 SD level of impairment in several cognitive domains.
4. Absence of delirium or other organic causes of cognitive impairment.

It is unlikely that a "perfect" criterion for MCI in PD will ever be proposed to the satisfaction of all experts in the field. The ranges of cognitive performance are only descriptive guidelines and do not imply specific cutoff scores. There will probably be a need, at some point, to specifically define what cognitive decline is from premorbid level of ability, factoring for "normal age-related decline" and that which is viewed as "acceptable decline" in PD.

The risk and rate of cognitive decline in PD can be variable depending on the population subset

Identified risk factors for dementia in PD include older age, later PD onset, male gender, longer durations of symptoms, specific aspects of cognitive dysfunction (eg, decreased verbal fluency), predominance of axial motor symptoms, and the presence of MCI (Marttila and Rinne 1976; Elizan et al 1986; Jacobs et al 1995; Mahieux et al 1998; Aarsland, Anderson, et al 2001; Levy, Jacobs, et al 2002; Levy, Schupf, et al 2002).

In a prospective cohort study, 250 non-demented patients with PD were evaluated for incident dementia after 5 years. Seventy-four of the patients became demented after 5 years. Odds ratios (OR) for incident dementia with PD were increased for the following: being older than 70 years of age (2.7; 1.4–5.5), having a UPDRS motor subscale score of greater than 25 (3.0; 1.5–6.2), being depressed (2.7; 1.5–6.6), being confused or psychotic on levodopa (3.3; 1.3–8.7), and interestingly, having facial masking as a presenting sign (6.1; 1.4–26.9) (Stern et al 1993).

Predicting and identifying the subset of a population that would most likely convert to dementia could be misleading. One study followed 647 geriatric subjects over 3 years to identify if "preclinical syndromes" for AD, vascular dementia, and PD-related dementias existed. Each subject was asked to participate in a medical assessment that included a standardized medical history, neuropsychological protocol, and physical examination. Preclinical syndromes for the three predominant dementias (AD, vascular dementia, and PD dementia) and their combinations were defined using cognitive, motor, and vascular features. In this study, preclinical syndromes were defined as having cognitive impairment displaying mild to moderate deficits in one or more areas of cognition but not meeting DSM-IIIR criteria for dementia; vascular features based on arteriopathy score (weighted points for the presence of atrial fibrillation, diabetes, hypertension, heart disease, claudication, hypercholesterolemia, and smoking history) and a vascular score (weighted points for the presence of cerebrovascular disease such as stroke and transient ischemic attacks); and extrapyramidal features based on an extrapyramidal score (rigidity, cogwheeling, slowed fine finger movements) and the presence of an extrapyramidal gait disorder. Preclinical syndromes affected 55.7% (299/647) and showed increased odds of developing dementia (OR: 4.81; $p < 0.001$). Although the presence of preclinical syndromes were highly sensitive at detecting 52 of 58 (89.7%) incident dementias, 268 (80.6%) of the subjects with preclinical syndromes did not show dementia over 3 years (positive predictive value of 19%). Subjects defined as having a combination of cognitive, extrapyramidal, and vascular features were at greatest risk of progressing to dementia (Waite et al 2001).

Can medications possibly influence performance on cognitive tests?

Common PD medications appear to influence performance on cognitive measures. Both impairments and improvements have been reported. For example, in an open-label randomized study of 28 right-handed patients with early/mild PD who obtained baseline and repeat

neuropsychological and clinical assessments during 3 treatment conditions: a baseline "off" treatment condition; an "on" with pramipexole (a dopamine agonist) condition; and an "on" with levodopa condition. In comparison to the baseline ("off" condition), when medicated with pramipexole, patients showed a significant impairment in short-term memory, attentional-executive functions, and verbal fluency. In contrast, these impairments were not observed with the "on" levodopa condition relative to baseline. Although not exceeding normative values, this study showed that various PD medications may influence cognitive functions or cognitive testing ability (Brusa et al 2003). Moreover, a decline in cognitive abilities has also been reported when there is medication withdrawal. Specifically, it has been reported that levodopa withdrawal in PD selectively impaired cognitive performance tests sensitive to frontal lobe dysfunction (Lange et al 1992).

Positive changes or improvements in cognitive functioning have been reported with other medications. For example, pergolide (another dopamine agonist) (Perachon et al 1999) and levodopa (Lange et al 1995) are reported to improve tests sensitive to frontal lobe dysfunction in PD patients. The difference in the cognitive effects between the 2 dopamine agonists (pramipexole and pergolide) is attributed to the sedative effect of pramipexole and the D1 receptor affinity of pergolide.

These findings speak to the importance of considering medications during the evaluation for cognitive changes in PD. When differences in cognitive decline are subtle, like that in PD patients with MCI, appreciating cognitive changes that may be due to medications is essential. Appropriately timing neuropsychological testing to on and off medication periods needs to be recorded for appropriate cognitive monitoring and MCI diagnosis.

The promise

The pathology in PD and AD, for which cholinesterase inhibitors are principally used, is similar

Cholinergic networks mediate aspects of memory and attention in animal and human studies, and are similarly damaged in PD and AD (Tiraboschi et al 2000). In autopsy series, striking cell loss is found in the nucleus basalis of Meynert. Additionally, choline acetyltransferase (ChAT) activity has consistently been reported to be decreased to approximately 40%–60% of control values in frontal, temporal, and hippocampal cortex. These changes were accompanied by a decrease in acetylcholinesterase (AChE) activity (Ruberg et al 1982; Perry et al 1991, 1993; Mattila et al 2001). In cases of PD with dementia, ChAT activity has been shown to be low in the neocortex compared with the hippocampus (Kuhl et al 1996). Cognitive impairment in these cases seemed to correlate significantly with both prefrontal ChAT activity ($r = -0.52$, $p = 0.005$) and the density of D1 dopamine receptors in the caudate nucleus ($r = -0.40$, $p = 0.037$) (Mattila et al 2001).

Nicotinic cholinergic receptor binding in the putamen is also decreased in PD (Martin-Ruiz et al 2002). However, muscarinic cholinergic receptors have been reported to be relatively spared in PD with dementia when compared with AD (Perry et al 1991). Therefore, from a theoretical point of view, there may be a strong rationale for testing cholinesterase inhibitors in individuals with PD (Aarsland et al 2002).

Cholinesterase inhibitors 'work' in cortical, subcortical, and mixed forms of dementia

Four members of this class of compounds are currently FDA-approved for the treatment of mild to moderate AD. Tacrine, donepezil, rivastigmine, and galantamine are all inhibitors of AChE enzyme and, in theory, help repair brain cholinergic deficits by increasing the amount of acetylcholine available for binding to cholinergic receptors in the synaptic cleft.

The pharmacokinetic properties and in vivo ability to modulate cholinergic networks of each of these compounds are somewhat different. Tacrine and rivastigmine inhibit a second enzyme, butryl cholinesterase, whose activity seems to be up-regulated in AD and may parallel senile plaque formation. Galantamine has additional properties as an allosteric modulator of presynaptic nicotinic cholinergic receptors.

Each of these compounds show comparable efficacy in maintaining the Alzheimer's disease Assessment Scale-cognitive portion (ADAS-cog) scores above baseline in double-blind controlled studies (Rogers and Friedhoff 1998; Rogers, Doody, et al 1998; Rogers, Farlow, et al 1998; Rosler et al 1999; Farlow et al 2000; Raskind et al 2000; Tariot et al 2000; Corey-Bloom 2003). Also, brain metabolism by fluorodeoxyglucose-positron emission tomography (FDG-PET) has been shown to increase in tandem with clinical benefit (Potkin et al 2001). In observational studies, long-term use of cholinesterase inhibitors translates into a 2-year

delay in admission to nursing homes (Winblad et al 2001; Lopez et al 2002). In a landmark long-term 5 mg–10 mg donepezil vs placebo randomized study by the AD2000 Collaborative Group (AD2000 2004), however, there was no significant reduction in symptom progression or institutionalization among AD patients. Clearly, additional long-term randomized studies investigating the benefits of pharmaceutical agents on disease progression are needed.

Interestingly, there have been increasing reports of benefit using AChE inhibitors for dementias that involve subcortical disease processes.

Erkinjuntti et al (2002) investigated the effects of galantamine on 592 patients with vascular or mixed (AD with cerebrovascular disease) dementia using the Alzheimer's disease assessment cognitive subscale (ADAS-cog) and the clinician's interview-based impression of change plus caregiver input (CIBIC-plus) as primary endpoints. In this study, galantamine showed greater efficacy than placebo on ADAS-cog (galantamine change –1.7 vs placebo +1.0; treatment effect 2.7 points; $p < 0.0001$) and CIBIC-plus (74% vs 59% remained stable or improved; $p = 0.001$).

Similary, there are several reports of rivastigmine and donepezil use in vascular and mixed dementia with comparable positive results (Kumar et al 2000; Moretti et al 2001, 2004).

Closer to PD pathology, positive effects of AChE have been reported in DLB. In a 23-week, prospective, randomized double-blind, placebo-controlled, multicenter study, 120 patients with DLB were given up to 12 mg of rivastigmine daily or placebo for 20 weeks followed by 3 weeks rest (McKeith et al 2000). Patients treated with rivastigmine showed statistically significant improvement in cognition as measured by the Cognitive Drug Research (CDR). Overall Speed score at week 12 ($p < 0.01$) and week 20 ($p < 0.05$). Rivastigmine showed a mean improvement of 1.5 points in the Mini-Mental State Examination (MMSE), while the placebo patients declined by a mean of 0.1 point at week 20 ($p = 0.072$). Moreover, patients taking rivastigmine were significantly less apathetic and anxious, and had fewer delusions and hallucinations while on treatment than controls. These significant improvements in behavior were measured by the scores on the 4-item Neuropsychiatric Inventory (NPI) ($p < 0.05$) and the 10-item NPI ($p < 0.01$).

Finally, the reported use of cholinesterase inhibitors among the cognitively-impaired PD population is slowly gaining momentum. The use of the first cholinesterase inhibitor, tacrine, in the AD population was accompanied by anecdotal evidence of worsened parkinsonism (184): reports of fulminant hepatotoxicity resulted in the addition of a warning label. Only a very modest clinical benefit was initially appreciated by clinicians using tacrine. Because of problems with tacrine, enthusiasm for larger trials of this class of compounds in PD was reduced. Nonetheless, a small open-label trial of this compound ($n = 7$) in PD patients with psychosis reported 5 patients with complete resolution and 2 patients with partial improvement of hallucinations. The mean MMSE score improved by 7.1 points and the UPDRS motor scores improved dramatically (Hutchinson and Fazzini 1996).

It was not until recently that investigators began to reconsider the potential of these compounds for treating dementia in PD (Geizer and Ancill 1998; Kaufer et al 1998; Shea et al 1998; Aarsland et al 1999; Lanctot and Herrmann 2000; McKeith et al 2000; Samuel et al 2000; Skjerve and Nygaard 2000; Grace et al 2001; Maclean et al 2001; Rojas-Fernandez 2001). This change was encouraged by slow confirmation of the more benign side-effect profiles of the remaining three cholinesterase inhibitors and reports of better efficacy in treating the cognitive and neuropsychiatric concomitants of DLB.

Another report, also an open-label study, consisted of eleven patients (average age 75 years) with PD dementia, who were treated for 26 weeks with either tacrine (7 patients) or donepezil (4 patients). For the combined group, scores for the ADAS-cog improved by 3.2 points ($p < 0.012$). No change in motor function as assessed by the Short Parkinson Evaluation Scale (SPES) was noted (Werber and Rabey 2001). Behavioral symptoms were not mentioned.

In an open-label trial of 12 PD patients with drug-induced psychosis (Reading et al 2001), rivastigmine was initiated at 1.5 mg bid (twice a day) and increased every 2 weeks until either the maximum of 6 mg bid or the highest tolerated dose was achieved. The drug was well tolerated. Three withdrew, one due to death from unrelated sepsis, one because the caretaker became ill, and the third from nausea. The MMSE improved from 20.8 to 25.4 while the UPDRS motor scale did not change. The mean NPI score improved on the subscales measuring hallucinations and sleep disturbances. Caregiver distress also improved. Repeat measurements after a 3-week withdrawal showed a comparable decline. No worsening of tremor or parkinsonism was noted.

Another open-label pilot study with rivastigmine has not yet been published in a peer-reviewed forum (Korczyn

2002). Nineteen patients "with severe PD associated dementia" were evaluated at baseline, after 26 weeks of treatment and following an 8-week washout period. The average dose from weeks 12 though 26 of treatment was approximately 7.5 mg/day. Significant changes in total ADAS-cog and the attention subscore of the MMSE (both $p < 0.004$) were reported, but the actual scores were not given. The comment was made that "enhancement of tremor was the only extrapyramidal symptom that worsened in some patients".

The results of the first randomized, double blind, placebo-controlled, crossover study were reported in 2002 (Aarsland et al 2002, 2003). Fourteen individuals with PD and cognitive impairment were assigned to either donepezil (5 or 10 mg/d) or placebo during two sequential periods lasting 10 weeks each. Patient characteristics at baseline included: a history of cognitive decline beginning one year or more after the onset of parkinsonism (3.0 ± 2.6 years); average duration of PD 10.8 ± 5.2 years; mean age 71.0 ± 3.9 years; and average levodopa dose 485 ± 256 mg/d. The average MMSE score at study entry was 20.8 ± 3.4, with all patients showing evidence of decline in memory and at least one other category of cognitive function. Significant effects of donepezil compared with placebo for MMSE (2.1 ± 2.7 vs 0.3 ± 3.2, $p = 0.013$) and the CIBIC (3.3 ± 0.9 vs 4.1 ± 0.85) were noted. Motor UPDRS subscores did not worsen during donepezil treatment. Three patients had improved scores on delusions, 2 on hallucinations, 1 on agitation, 6 on depression, and 5 on apathy. None of these improvements were statistically significant due to the low scores on these items at baseline and the small number of subjects involved.

The same group of authors reported their findings on 16 PD patients with dementia who were treated open-label with galantamine (Aarsland et al 2003). Improvement in global mental symptoms was noted in 8 patients, whereas worsening was noted in 4. Hallucinations improved in 7 of the 9 patients (all with hallucinations before treatment). Parkinsonism improved in 6, but a mild worsening of tremor was noted in three. Clock drawing improved ($p = 0.0016$) (Agid et al 1986; Aarsland, Bronnick, et al 2001, 2003).

In addition, two small case series targeting individuals with PD and dementia with psychosis had recently been added to the literature. The first involved 6 individuals treated with donepezil up to 10 mg/day for 6 weeks of treatment, without obvious deterioration of parkinsonian symptoms (Bergman and Lerner 2002); the second, used rivastigmine (Bullock and Cameron 2002). Neither study noted obvious deterioration of parkinsonian symptoms or paradoxical worsening of behavior.

Table 3 Agents currently being tested in mild cognitive impairment states

Agent	Outcome measurement	Study duration
Donepezil	Change in cognitive function	6 months
Donepezil	Conversion to AD	36 months
Galantamine	Conversion to AD	24–36 months
Rivastigmine	Conversion to AD	24–36 months
Rofecoxib	Conversion to dementia	24–36 months
Vitamin E	Conversion to AD	36 months
CX-516	Change in cognitive function	1 month
Piracetam	Change in cognitive function	12 months

Abbreviation: AD, Alzheimer's disease.

MCI can be identified and successfully followed

As an example, one multicenter study followed 769 patients with MCI: 107 cognitively normal elderly controls, and 122 patients with very mild AD (Clinical Dementia Rating, CDR = 0.5); 183 patients with mild AD (CDR = 1.0) to determine whether vitamin E or donepezil was effective at delaying the time to a clinical diagnosis of AD (Grundman et al 2004). ADAS-cog scores were 5.6 +/–3.3 for controls, 11.3 +/–4.4 for patients with MCI, 18.0 +/–6.2 for AD CDR group 0.5, and 25.2 +/–8.8 for the AD CDR group 1.0. Moreover, patients with MCI had hippocampal volumes that were intermediate between those of controls and patients with AD. The authors concluded that patients with MCI were intermediate between clinically normal individuals and patients with AD on cognitive, functional, and radiological ratings. It demonstrated the successful implementation of operational criteria for this group of at-risk patients in a multicenter clinical trial.

Table 3 outlines the agents currently being tested in MCI states. Computerized cognitive assessment systems are now being used for its ease and low cost in longitudinal testing, especially in MCI states. Validation studies are able to classify individuals as cognitively healthy, MCI, or mild AD on the basis of computerized cognitive tests (Doniger et al 2003).

The state of MCI in various types of dementia has recently been investigated more carefully. The Mayo Clinic Registry identified 21 patients with clinically probable DLB who had been previously characterized as having MCI. Similar to that predicted in PD, the previous MCI states prior to DLB were heterogeneous. Ten patients had the amnestic form of MCI, 6 had single non-memory domain

MCI, 4 had multiple domain MCI with amnesia, and 1 with multiple domain MCI without amnesia. The authors then concluded that unlike AD, where the majority of patients evolved from an amnestic form of MCI, each of the MCI subtypes could convert into DLB.

MCI states even among elderly patients with vascular risk factors are also becoming recognized (Geroldi et al 2003).

Biomarkers may help in identification and longitudinal follow-up of MCI patients

In AD, it has been recognized that as cognitive impairment worsens from normal to MCI to full-scale dementia, hippocampal volume inversely decreases (Xu et al 2000). One study classified 80 patients with MCI into 3 groups according to their hippocampal volume: >50th percentile, <50th percentile, and <1st percentile compared with normal controls. During the period of longitudinal observation, which averaged 32.6 months, 27 of the 80 MCI patients became demented. Hippocampal atrophy at baseline was significantly associated with crossover from MCI to AD (relative risk 0.69, $p = 0.015$). Moreover, the risk for conversion to full dementia in the next 5 years followed 3 separate curves, the steepest coming from the group with hippocampal volumes <1st percentile from the normal controls (Jack et al 1999).

This anatomical marker had also been described in PD and parkinsonism (Camicioli et al 2003). One study compared the hippocampal volumes between 10 PD, 10 PD patients with MCI or dementia, 11 AD, and 12 controls. The "effect sizes" compared with the control group were: 0.66 for the PD group, 1.22 for the PD group with cognitive impairment, and 1.81 for the AD group. The authors concluded that progressive hippocampal volume loss in PD paralleled cognitive impairment. They felt these findings could be quantitated and could provide an early marker for dementia in PD (Camicioli et al 2003).

Rates of cerebral atrophy have been correlated with measures of cognitive decline in PD. Serial volumetric T-1 weighted MRI on 8 non-demented PD vs 10 age-matched controls was performed. PD patients had reduced annual brain volume loss compared with controls ($p < 0.001$). Also, a significant correlation was seen between reduction in brain volume and reduction in performance IQ ($r = 0.84$; $p = 0.004$) and full scale IQ ($r = 0.63$; $p = 0.049$) (Hu, White, Chaudhuri, et al 2001; Hu, White, Herlihy, et al 2001).

Some cognitive tests can be sensitive enough to detect cognitive impairment even in early PD

Many studies have now established that patients with PD develop mild neuropsychological deficits across a range of cognitive functions (Lees and Smith 1983; Boller et al 1984; Weingartner et al 1984; Taylor et al 1986, 1987; Sagar, Cohen, et al 1988; Sagar, Sullivan, et al 1988; Pillon et al 1996). However, not all neuropsychological tests are equally sensitive in detecting MCI in PD or in following progression

Table 4 Cognitive tests reported to be sensitive in detecting subtle changes in Parkinson's disease

Cognitive domain	Test	Author
Visuoperception impairment	Visuoconstructional ability, eg, Rey-Osterrieth Complex Figure	Freeman et al 2000
	Visuospatial, eg, Raven's Progressive Matrices	Farina et al 2000
	Face recognition memory	Levin et al 1989; Levin 1990; Haeske-Dewick 1996; Cousins et al 2000
	Spatial memory	Levin 1990; Pillon et al 1996; Giraudo et al 1997; Pillon et al 1997; Postle, Jonides, et al 1997; Postle, Locascio, et al 1997
Learning and memory deficits	Procedural learning	Vakil and Herishanu-Naaman 1998; Koenig et al 1999
	Incidental (not intentional) new learning of verbal material	Ivory et al 1999
	Delayed recognition memory	Stebbins et al 1999
	Explicit memory	Appollonio et al 1994
	Free recall	Breen 1993
Attentional deficits	Disinhibition of automatic word reading	Henik et al 1993
	Attentional set-shifting ability	Owen et al 1992
General cognitive test	Weschler Adult Intelligence Scale–Revised as a Neuropsychological Instrument (WAIS-RNI)	Peavy et al 2001

of cognitive impairment in PD (Jacobs et al 1995). Table 4 lists the neuropsychological tests reported to be sensitive in detecting subtle cognitive changes in PD. Some cognitive tests are consistently unimpaired in early PD such as Digit Span, Information, and Boston Naming Test; while some neuropsychological tests show mixed reports, such as Logical Memory, Associate Learning, Word Fluency Test (Levin et al 1989; Cooper et al 1991; McFadden et al 1996; Ross et al 1996; Kuzis et al 1997, 1999).

At the University of Florida Movement Disorders Center, a retrospective analysis comparing the neuropsychological profile of random PD patients to their "on" UPDRS-Motor scores was performed. The complete neuropsychological profile performed in the "on" state included the MMSE, Dementia Rating Scale (DRS); and tests for general intelligence (WAIS 3, Vocabulary subtest); attention and concentration (Digit Span); Verbal Memory (HVLT, WRAT); language (Boston Naming, Controlled Oral Word Association Test); visual-spatial (Judgment of Line Orientation, Facial Recognition Test); and executive function (Stroop, Trail Making Test). The cognitive profiles of 60 PD patients (43 males and 17 females), with a mean age of 68 years (range: 51–88), and an average of 15 years of education (range: 9–21) were analyzed. MMSE ($r = -0.73$; $p < 0.001$), DRS ($r = -0.45$; $p < 0.001$), and most test scores in all cognitive domains were inversely correlated to the UPDRS motor scores. In addition, a significant association was found between the UPDRS motor scores and MMSE ($r^2 = 0.480$; $F(1, 51) = 47.08$; $p < 0.001$) or DRS ($r^2 = 0.205$; $F(1, 51) = 13.1$; $p < 0.001$), independent of age and level of education. In this cohort, cognitive impairment paralleled motor deterioration (Fernandez et al 2003).

Cholinesterase inhibitors may delay cognitive decline even among demented patients

There are at least 2 long-term, multicenter studies that suggested the early use of AChE inhibitors could offer sustained and greater benefits compared with delayed treatment. In one study, 158 patients with AD who originally participated in a double-blind, placebo-controlled multicenter trial using rivastigmine, agreed to continue on the open-label phase (Doraiswamy et al 2002). The rivastigmine groups (originally randomized to 1–4 or 6–12 mg/day) experienced significantly smaller declines in ADAS-cog scores from baseline than the projected placebo group after 52 weeks. Patients receiving rivastigmine experienced significantly less decline compared with patients originally receiving placebo and then initiating rivastigmine treatment after a 6-month delay.

Similarly, in the 6-month, double-blind, multicenter study using galantamine in AD followed by a 6-month open-label phase, subjects who were initially randomized to placebo never caught up in their ADAS-cog scores at the end of the 6-month open-label phase compared with the subjects who were initially randomized to galantamine (Raskind et al 2000).

The solution

Two traditional schools of research, divergent yet complementary, contribute to scientific advancement: the 'microscopic' and the 'macroscopic' approach. Understanding MCI through the microscopic approach often uses smaller-scale, hypothesis-driven studies on a subset of cognitively-impaired PD patients or a specific aspect (eg, pathology, genetics, functional anatomy) of MCI. This approach seeks to understand the basic defect(s) in MCI and tries to determine what triggers the cascade of progressive, irreversible cognitive decline, obtaining small pieces of information until the entire puzzle is solved. From the present review of literature, it is clear that there is a need to develop more accurate biomarkers or predictors of cognitive impairment; a better identification and delineation of the roles of various neurotransmitters; a clearer understanding of basal ganglia circuitry and how it contributes to dementia in PD; and a system of sorting out the overlapping pathology of dementia subtypes. More autopsy reports from patients with MCI are needed. Negative reports and anecdotal cases are required to help to fill an important vacuum of knowledge. The macroscopic approach is favored by a clinical trialist who seeks to understand a process from a more panoramic perspective. It attempts to learn how MCI progresses, and which sub-population progresses slower or faster, and how evolution to full dementia can, thus, be prevented. Although it may still be premature, the present literature, can similarly guide us in developing a well designed, placebo-controlled, parallel-group, multicenter trial on MCI in PD. Given the information we have to date, the "ideal" multicenter study testing an agent's potential in slowing disease progression should have the following characteristics:

1. *The inclusion criteria of MCI in PD should be strict but must encompass all subtypes of MCI*. Given the pathologic and radiologic heterogeneity of dementia in PD, the MCI subtypes that eventually progress to dementia, just like that of DLB, is also probably

heterogeneous. Thus, a multicenter or longitudinal trial that confines its inclusion criteria to only specific subtypes of MCI are mostly likely unable to represent the true picture of cognitive decline in PD.

2. *The study should be large enough*. Because the rate of progression and the degree of treatment response of each MCI subtype that leads to PD dementia is unclear, the ideal study requires a large sample.
3. *The study duration should be long enough to see a "separation".* Since the cognitive decline is progressive and the success of a treatment is measured by a slower decline or the delay (or prevention) of certain neurobehavioral features (eg, psychosis) rather than improvement in cognition, the study should be of sufficient duration to see a divergence of treatment groups over time. Results of studies involving smaller samples and/or shorter periods of observation are more likely to lead to a false statistical interpretation.
4. *The inclusion criteria for idiopathic PD should be stringent.* Careless addition of cases of essential tremor, multiple systems atrophy, progressive supranuclear palsy, and DLB will make interpretation challenging, especially when cognitive changes from year to year are too subtle to clinically or even statistically appreciate.
5. *Choose the specific tests wisely in the neuropsychological protocol*. Not all neuropsychological tests are equal in sensitivity in detecting subtle cognitive impairment, especially in PD. Some cognitive domains are more affected than others in PD, and only certain neuropsychological tests within that cognitive domain are able to measure minimal cognitive changes.
6. *Consider using a biomarker*. Not all biomarkers are equal. Functional biomarkers, such as SPECT and PET scans, may be difficult to use because of the heterogeneity in the blood flow patterns of PD patients with dementia or MCI. Anatomical markers such as hippocampal volume measurement seem to be more consistent. Better biomarkers are needed.
7. *The timing of neuropsychological tests should be uniform in relation to drug intake.* Most common drugs such as pramipexole and levodopa can have opposite effects in neuropsychological test performance. Similarly, the "on" and "off" state of a PD patient can equally influence performance. When differences are subtle and are appreciated only when measured over time, controlling for environmental factors is essential.
8. *Consider outcome measures that will speak to the pragmatic use of drugs.* The recent large-scale randomized study on donepezil vs placebo completed by the UK AD2000 Collaborative Group (AD2000, 2004) demonstrates the importance of including appropriate pragmatic outcome measures for clinical trial research. Such outcome measures include changes in comorbidity status, caregiver level of burden, psychiatric and behavioral symptoms, institutionalization, and formal care costs.

In summary, the best chance of halting a progressive illness like cognitive decline/MCI in PD will be through discovery and experimentation at the earliest possible time, and will be accomplished by simultaneously employing both micro- and macroscopic approaches.

Disclosures

Over the past 5 years, Hubert H Fernandez, has been a paid consultant, paid speaker, or performed clinical research under contract with: Astra-Zeneca, Aventis, Novartis, Teva, Glaxo Smith Klein, Elan, MylanBertek, Cephalon, Amarin, Boehringer Ingelheim, Kyowa, Boston Life Sciences, and Merck KgaA. HF has no owner interest in any pharmaceutical company. Michael Okun, Dawn Bowers, Greg Crucian, and Catherine Price have no conflict of interest or outside relationships with pharmaceutical or other companies.

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