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Strengths and Challenges in Conducting Clinical Trials in Parkinson's Disease Mild Cognitive Impairment

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ABSTRACT: Treatments to slow the progression of cognitive dysfunction to dementia and improve the quality of life of persons with Parkinson's disease (PD) are desperately needed. Because PD mild cognitive impairment is considered a transitional stage before dementia, it opens a window to timely intervention. This article critically reviews the strengths and challenges of pharmacologic and nonpharmacologic clinical therapeutic trials in PD

mild cognitive impairment conducted during the past 5 years, including ongoing trials. Relatively few high-quality trials have been conducted, and some important factors in designing future clinical trials are discussed. © 2018 International Parkinson and Movement Disorder Society

Key Words: mild cognitive impairment; Parkinson disease; clinical trials; pharmacologic; nonpharmacologic

A symptomatic treatment for patients with Parkinson's disease with mild cognitive impairment (PD-MCI) that can significantly influence the quality of life of patients and families is of great interest to the PD community. Moreover, because PD-MCI is a transitional state to PD dementia (PDD), treatments are urgently needed to slow its progressive conversion to PDD.

Unfortunately, there have been limited advances in the development of therapeutics that can symptomatically improve PD-MCI. In addition, agents that could modify the progression have not been identified, and disease-modifying therapeutic trials aimed at PD-MCI are practically nonexistent. Some of the reasons that explain the lack of therapeutic progress are the following: (1) variable expression (both between and within

patients over time) of underlying pathologies involving isolated or combined cortical Lewy bodies, Alzheimer's disease (AD) pathology, or ischemic lesions, among others; (2) involvement of various cortical and subcortical networks and neurotransmitters; (3) only recent scientific recognition of the role of cognition in PD; (4) only recent development and validation of standardized PD-MCI diagnostic criteria; (5) heterogeneous cognitive phenotypes; and (6) lack of optimal cognitive outcome measures (see previous articles in this miniseries).

In this article, we critically review the strengths and limitations of pharmacologic and nonpharmacologic clinical therapeutic trials conducted in the past 5 years to improve cognition symptomatically and to slow the disease progression of PD-MCI, including ongoing PD-MCI therapeutic trials. Based on this review, we discuss important factors to consider when designing future clinical trials in this area.

Methodology

To review the past 5 years' literature, we conducted Medline searches using the search words «Parkinson's disease» and «MCI» or «cognitive impairment» and «clinical trials» or «randomized, therapeutic trials», «disease-modifying therapeutic trials», and reviewed

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the reference lists of these and review articles. To review ongoing trials, we searched “ClinGov” (clinicaltrials.gov).

Symptomatic Therapeutic Approaches

Nonpharmacologic Clinical Trials

Nonpharmacological therapies for cognitive difficulties in PD fall into the following 3 broad categories: cognitive interventions (including cognitive stimulation, cognitive training, and cognitive rehabilitation), physical exercise, and noninvasive brain stimulation (transcranial direct current stimulation [tDCS] and repetitive transcranial magnetic stimulation [rTMS]). Although studies seem to have used cognitive intervention terms such as cognitive training and rehabilitation almost interchangeably, the terms have been associated with specific methods.¹ Cognitive stimulation involves the engagement of persons (most often in groups) in general cognitive and social activities thought to promote and enhance function. In contrast, cognitive training involves guided practice (individually or in groups) on tasks (computerized or pencil and paper) or mnemonic strategies presumed to rely on and strengthen specific cognitive functions such as attention. Cognitive rehabilitation refers to individualized treatments that consider patient strengths, weaknesses, preferences, and goals and use both internal (eg, imagery) or external (eg, alarm) compensatory strategies.

The earliest studies seeking to enhance cognition in PD evaluated various, usually poorly specified, computerized cognitive training (CT) methods for executive dysfunction in unblinded, uncontrolled, small sample size studies,^{1,2} and initial reviews published approximately 5 years ago concluded that there was little empirical evidence to support such interventions.^{3,4}

The sophistication of more recent studies has been greater, but many of the studies carried out even in the past 5 years have numerous methodological limitations.⁵ Perhaps the biggest limitation, for the purposes of this review, is that few studies included persons with PD specifically diagnosed with cognitive impairment or with the more rigorous Movement Disorders Society criteria for PD-MCI.⁶ In addition, given the heterogeneity of cognitive impairments in PD,^{7,8} frequently used descriptors such as “nondemented” or “without dementia” (and in several instances no description of cognitive status) leave in doubt the nature and severity (phenotype) of the cognitive difficulties treated. The common practice of defining inclusion criteria via Mini-Mental State Examination (MMSE) cut-off scores fails to enlighten about cognitive status given the scale’s brevity, narrow focus, and established lack of sensitivity to PD-MCI.^{8,9}

Bearing in mind the limitation that most studies do not examine the effect of interventions on PD-MCI specifically, it is still helpful to consider what impact

nonpharmacological therapies have on cognition in PD “without dementia.” In the 2013 systematic review of nonpharmacological cognition enhancement studies in PD with and without cognitive impairment (not necessarily controlled or randomized) by Hindle and colleagues,¹⁰ 5 studies of CT, 5 studies of exercise and physical therapy, 3 studies of combined treatments, and 5 studies of noninvasive brain stimulation were identified as meeting inclusion criteria (a total of 18 studies or case series). Note that conflicting numbers for each type of included study are presented in the article abstract and Figure 1 in Hindle and colleagues.¹⁰ In only 6 of the reviewed studies were effect sizes associated with treatment available, and only 9 studies involved randomization. The authors concluded that only 1 small sample, randomized clinical trial¹¹ of CT warranted a quality rating of 1+ per the National Institute for Health and Clinical Excellence evidence-level guidelines.¹² In addition, they cautiously concluded that there is the suggestion that nonpharmacologic interventions may improve executive functions, but the quality evidence is lacking.

A total of 3 more recent (2015, 2017) quantitative meta-analyses have been published, 1 dealing with CT,¹³ 1 dealing with noninvasive brain stimulation,¹⁴ and the other with CT and noninvasive brain stimulation¹⁴ in PD (see Table 1 for a characterization of these studies and effect sizes related to treatment of cognition). These meta-analyses, it must be emphasized, contain studies using quite heterogeneous interventions and outcome measures. Furthermore, 1 of the meta-analyses¹⁴ reported effect sizes only for significant findings, making the range of effect sizes reported potentially very misleading. At best, the data at hand provide tentative support for the feasibility of nonpharmacologic intervention in PD (especially with regard to the enhancement of executive functions). Methodological limitations, many of them expertly discussed by Lawrence and colleagues,¹⁵ leave more questions unaddressed than addressed by the existing literature, and recent meta-analytic findings do not substantially alter the conclusions reached by Hindle and colleagues.¹⁰

Paul’s (1967)¹⁶ iconic question regarding psychotherapy outcome research: “What treatment, by whom, is most effective for this individual with that specific problem, and under which set of circumstances?”¹⁰ seems equally relevant 50 years later when contemplating the effects of (and designing research into) cognitive interventions in PD. Perhaps given new technologies available for nonpharmacological intervention, one also needs to inquire about treatment “with what” and “for how long?” Additional preliminary studies of other nonpharmacologic intervention for cognitive dysfunction in PD are underway (see Supplementary Table), but detailed, large randomized

TABLE 1. Characteristics and treatment effect sizes reported by recent meta-analyses of cognitive training, rTMS and tDCS effects on cognition

Variable	Leung et al, 2015 ¹³	Lawrence et al, 2017 ¹⁵	Dinkelbach et al, 2017 ¹⁴
Treatments evaluated	CT	CT, rTMS, tDCS	rTMS, tDCS
Number of studies included	7 CT	11 CT (8 standard, 3 individualized) 3 rTMS 0 tDCS	13 rTMS (3 cognition, 5 mood, 5 cognition + mood) 6 tDCS (1 cognition, 1 mood, 4 cognition + mood)
Total number of subjects in included studies	272 CT: 133 Controls: 139	480 rTMS: 74 CT: 406 (standard 315; individualized 91) Active treatment vs control not reported	561 rTMS: 455 tDCS: 106 Active treatment vs control not specified
Publication cutoff date of studies reviewed	November 6, 2014	May 27, 2016	February 16, 2016
Study inclusion criteria (specified in article)	Behavioral outcome measure: cognition, instrumental activities of daily living, depression, quality of life At least 4 hours of CT CT comprised at least 50% of intervention if combined treatment	Idiopathic PD per UKPDS Brain Bank criteria rTMS, tDCS, or CT intervention controlled study outcome measured by standardized neuropsychological test(s) data available to calculate effect size Hedges <i>g</i> reflecting improvement in treatment group from baseline relative to control	Randomized, placebo-controlled idiopathic PD diagnosis At least one outcome measure of cognition OR mood At least 5 subjects per group
Definition of effect size	Hedges <i>g</i> reflecting improvement in treatment group from baseline relative to control. Small: $g \leq 0.30$; moderate: $0.30 < g < 0.60$; large $g \geq 0.60$; + indicates gain, - indicates decrement		Cohen's <i>d</i> ; no further detail provided
Standard CT effect sizes	N/A	Executive: 0.51 Attention/working memory: 0.29 Memory: 0.35 Visuospatial function: 0.32 Global cognition: 0.32 Executive: 0.30 Attention/working memory: 0.08 Memory: 0.28 Visuospatial function: -0.15 Global cognition: 0.28	N/A
Individualized CT effect sizes	N/A		N/A
Overall CT effect sizes	Overall: 0.23 Global cognition: 0.32 Executive functions: 0.30 Processing speed: 0.31 Working memory: 0.74 Memory: 0.13 Visuospatial skills: 0.01 Depression: 0.50 Attention: -0.13 Instrumental ADL: 0.01 Quality of life: -0.10	Executive: 0.42 Attention/working memory: 0.23 Memory: 0.33 Visuospatial function: 0.25 Global cognition: 0.32	N/A

(Continued)

TABLE 1. Continued

Variable	Leung et al, 2015 ¹³	Lawrence et al, 2017 ¹⁵	Dinkelbach et al, 2017 ¹⁴
Overall rTMS effect sizes	N/A	Executive: 0.40 Attention/working memory: 0.34 Memory: N/A Visuospatial function: N/A Global cognition: -0.17	Cognition evaluated in 8/13 studies, usually with 1-2 tests. Effect sizes only reported for individual tests showing significant change and only for 3/8 cognitive studies. Treatment effect sizes ranged from 0.23 to 0.57 for reported cognitive measures (eg, Stroop task, verbal fluency)
Overall tDCS effect sizes	N/A	N/A	Cognition evaluated in 5/6 studies with a variety of tests. Effect sizes only reported for individual tests showing significant change: range -1.52 to 1.45.
MCI studies only	Not defined	No	No
Controlled studies only	Yes	Yes	Yes
Randomized, controlled studies only	Yes	No	Yes

CT, clinical trials; MCI, mild cognitive impairment; N/A, not applicable; tDCS, transcranial direct current stimulation; rTMS, repetitive transcranial magnetic stimulation.

clinical trials are probably some distance and time away, if preliminary studies prove fruitful. For example, 2 small trials of nucleus basalis of Meynert deep brain stimulation (DBS) and subthalamic or pallidal DBS are underway in Phoenix and London based on encouraging results in a prior case report.¹⁷ Gratwicke and colleagues¹⁸ reported a sham-controlled crossover bilateral DBS of the Meynert nuclei study in PD patients with dementia and showed that this procedure was safe, but the primary cognitive outcomes did not significantly improve. However, there was an improvement in the neuropsychiatric inventory.

Although patients in many studies using neuromodulation are nominally blinded to intervention (eg, sham rTMS vs active rTMS), in practice it is difficult to blind patients to active treatment (eg, in cognitive training vs general activity, aerobic vs nonaerobic exercise, DBS). Consequently, it is important to assess effectiveness of the blind, which is rarely reported. Some creativity may be needed in selecting control groups in DBS. Although blinding as to target may be possible, blinding to DBS versus best medical therapy is more challenging (although raters can be blinded to treatment by use of, for example, bandages over a patients' head). Recent studies have used a delayed stimulation condition, which means both active and control groups have had surgery, and ineffective stimulation levels can be used to mask active treatment. In cognitive training, it will be important to identify crucial elements of the treatment via the systematic addition of treatment components or their selective elimination, although carry-over effects present a challenge, especially because duration of treatment effects is unknown (also a challenge in crossover designs).

Pharmacologic Symptomatic Clinical Trials

We reviewed studies, including 5 placebo-controlled trials,¹⁹⁻²³ that totaled 680 patients (Table 2); 2 therapeutic trials with rivastigmine, 3 with rasagiline, and 2 with atomoxetine. We categorize the studies by the neurotransmitter system that was intended to be modified by the intervention.

Acetylcholine. Cholinergic deficit is evident early in PD, thus cholinesterase inhibitors may be useful at predementia stages. In the first placebo-controlled pilot trial in PD-MCI, the rivastigmine patch (maintenance dose 9.5 mg/d) was given to 28 patients in a crossover trial with 2 10-week treatment periods separated by a 4-week wash-out period. There was a non-significant trend on the primary end-point, the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change scale. Of note, the difference on this scale (0.46) was similar to that observed in the large (n = 541) pivotal rivastigmine trial in patients with PD dementia (0.5).²⁴ Moreover, secondary analyses showed a significant effect on the

TABLE 2. Pharmacologic symptomatic clinical therapeutic trials reviewed

Author	Year	Population	N included	Active drug	Dose, mg/d	Design	Duration, weeks	Prim outcome	Second outcomes	Results
Mamikonian et al ²²	2015	PD-MCI	28	Rivastigmine	9.5/24 hrs	RCT-crossover	24 (10 + 4 + 10)	CGIC	MoCa, DRS, ECB	Trend on CGIC, sign effect on ECOG
Weintraub et al ^{19a}	2016	PD-MCI	170	Rasagiline	1	RCT	24	SCOPA-COG	MOCA, CIBIC, ADL	No sign cognitive effects on primary or secondary outcomes
Weintraub et al ²⁷	2010	PD-DEP	55	Atomoxetine	80	RCT	8	IDS & CGIC	MMSE	Sign effect on MMSE, 1.3 points diff
Li et al ²¹	2016	PD-CI/PD-NC	41	Rivastigmine	6	RCT	52	MOCA, falls		Not reporting findings separately in MCI Positive effect on COG and se-phospholipids, no change in UPDRSII
Hinson et al ²⁹	2016	MCI	30	Atomoxetine	80	RCT	10	Cognitive tests		No sign test effects, but on subj scales
Smith et al ^{26a}	2015	De novo PD treated with antidepressant	191	Rasagiline	1 or 2	RCT	36	UPDRS cognitive subscale		Significant positive effect
Hanagasi et al ²⁵	2011	PD-MCI	55	Rasagiline	1	RCT	12	Further support for the use of atomoxetine or other noradrenergic agents was provided in a single-dose, placebo-controlled study, which showed that 40 mg atomoxetine improved selected tests of decision-making and attention in PD185		
Ondo et al ²⁰	2011	PD nondemented	40	Memantine	20	RCT	8	Nonmotor scales, including Conner attention test		No significant results

Analyses based on the 48 completers. Less worsening of cognition in rasagiline group. CI, cognitive impairment; CGIC, Clinical global improvement or change; DEP, depression; IDS, Inventory of Depressive Symptoms; MCI, mild cognitive impairment; NMs, nonmotor symptoms; RCT, randomized clinical trial; SCOPA-COG, the Scales for Outcomes in Parkinson's disease-COGnition.

^aSecondary analysis.

Everyday Cognition Battery functioning scale, which assesses function on 39 cognitive functioning items, and a numerical effect on the Montreal Cognitive Assessment (MoCA), a cognitive screening test including items relevant to PD.²² The rivastigmine patch was well tolerated. A larger, placebo-controlled study for 18 months of 176 PD patients reported positive effect on the MoCA using rivastigmine capsules 6 mg/d, but this study included a mix group of PD patients with normal cognition, MCI, and dementia and did not report findings in each group separately.²¹ There is an ongoing 48-week study of donepezil in PD-MCI (Clinicaltrials.gov, NCT02450786).

Dopamine. There is theoretical and preliminary empirical evidence supporting the hypothesis that rasagiline, a selective Monoamino oxidase-B (MAO-B) inhibitor that enhances central dopamine transmission, may also have a positive cognitive effect. In an early exploratory study including 55 PD-MCI patients for 12 weeks, significant positive effects on rasagiline were found on several of the 25 neuropsychological tests and 1 (attention) of 5 composite cognitive domain scores. There was no global cognitive test, clinical change, or activities of daily living scores reported.²⁵ A subsequent larger placebo-controlled randomized trial for 24 weeks that included 170 PD-MCI patients did not show significant effects of rasagiline on the primary outcome, a summary cognitive score, or on any of the secondary measures, the MoCA test, or clinical impression of change.¹⁹ A secondary analysis of the ADAGIO rasagiline therapeutic trial, including only on the 191 de novo PD patients who were taking antidepressants, demonstrated positive effects after 36 weeks on a number of nonmotor symptoms based on the Unified Parkinson Disease Rating Scale (UPDRS), including cognition, with scores 0 to 4. Of note, no cognitive tests were used in this study.²⁶

Another study of rasagiline in PD-MCI is reported as completed on the ClinGov website, but results have been reported only in abstract form without sufficient level of detail.

Norepinephrine. In a study including depressed PD patients with MMSE score >14, atomoxetine, a selective norepinephrine reuptake inhibitor, was tested for possible antidepressant effects and was associated with significant effects on the MMSE, which was 1.3 points higher in the active group when compared with placebo after 8 weeks of treatment.²⁷ These findings were supported in a single-dose study that showed that atomoxetine improved selected tests of decision making and attention in PD.²⁸ However, in a subsequent study for 10 weeks with 30 PD-MCI patients,²⁹ no significant differences were found for the primary outcome (a battery of executive tests) or secondary analyses, including nonexecutive cognitive tests and mood

and anxiety scales. However, significant improvements were observed in the subjective scales of attention and impulsivity in the active group, but not in the placebo group.

Glutamate/NMDA. Memantine, a partial N-methyl-D-aspartate (NMDA)-antagonist approved for moderate and severe AD, was compared with placebo after 8 weeks in 40 nondemented PD patients. None of a battery of nonmotor tests, including a subjective attention test, showed significant improvement.²⁰

In summary, there is no robust evidence of positive cognitive effects in PD-MCI in the 8 placebo-controlled studies of agents affecting acetylcholine, dopamine, noradrenaline, or NMDA receptors. Typically, promising evidence from an early small trial is not supported in subsequent larger and more rigorous trials. Most of the studies were underpowered, with only 2 studies including >100 patients, only 5 specifically included patients with PD-MCI, and 1 included depressed patients. The outcome measures varied, and several did not report effects on cognitive summary scale or clinical impression of change. Thus, there is yet no robust evidence supporting symptomatic drug treatment of PD-MCI. There are, however, some promising findings for rivastigmine and atomoxetine, and an adequately powered trial with 1 or both of these agents is warranted. Not all PD patients with MCI may progress to dementia, and some might even revert to normal cognition. Thus, biomarkers to identify which PD-MCI patients have a progressive cognitive decline is a priority and should be employed to enable more homogeneous cohorts.

Disease-Modifying Clinical Trials for Nondemented Patients

Nonpharmacologic

Large, well-designed studies are needed to examine the utility of nonpharmacologic therapeutic trials in preventing cognitive decline. Of note, in a clinical trial³⁰ that assessed whether a 2-month, multidisciplinary, task-oriented, rehabilitation intervention, including motor, cognitive-behavioral, and occupational therapy, could modify the disease course of nondemented PD patients, the study did not even include a cognitive outcome measure.

Pharmacologic

The success of disease-modifying therapies for PD-MCI depends on identifying appropriate ways to overcome the difficulties related to the heterogeneity of the cognitive and underlying pathology and etiopathogenesis of the disorders. Moreover, it remains elusive to find neuroprotective therapies that can slow or stop the disease progression of PD and all other

neurodegenerative disorders, despite improved understanding of their etiopathogenesis.

The first, and only still, PD-MCI placebo-controlled neuroprotective trial²³ investigated whether the combination of creatine and coenzyme Q10 (CoQ10) could improve cognition by enhancing the mitochondria function and energy metabolism and protect against oxidative stress damage. This 18-month study randomized 75 PD-MCI patients who met the Movement Disorders Society PD-MCI criteria to either 10 gm/day of monohydrate creatine and 300 gm of CoQ10 or placebo. The cognitive outcome measure was the MoCA, and the biomarker was plasma phospholipid levels, a measure of cell membrane integrity. After 12 and 18 months of treatment, the MoCA scores and the plasma phospholipid levels improved in the combination therapy group. Although the average MoCA score of the combined therapy group decreased by only 1.6 points on average, the score of the control group decreased by 6.3 points. The combination of creatine and CoQ10 also reduced plasma phospholipid levels. Overall, this was a well-designed, randomized, placebo-control study. The authors reported study inclusion and exclusion criteria, methods of randomization, and a lack of between-group differences in demographics or overall cognition at baseline. However, they did not report whether there were drop-outs or side effects and unfortunately did not explore any other neuropsychological measures. If confirmed in larger studies, these study findings suggest that the combination of these 2 antioxidants could delay the decline of cognitive function in PD-MCI patients. However, one needs to be cautious with the possible benefits from only 1 study, especially considering that despite initial studies that showed the potential neuroprotective effect of CoQ10 in PD, a subsequent phase III, multicenter, placebo-controlled, randomized study had to be terminated earlier because of the lack of benefits.³¹

It is important to stress that despite the known prevalence and importance of PD-MCI,³² previous (ie, CoQ, MODERATO study) and ongoing (ie, STEADY-PD [NCT02168842] and SURE-PD [NCT02642393]) PD disease-modifying clinical trials are still not determining whether the enrolled PD patients fulfill the PD-MCI diagnostic criteria or use as secondary outcome measures cognitive testing or conversion into PD-MCI or PDD. It is expected that future neuroprotective studies would focus on PD-MCI specifically, if not even earlier in the process of cognitive decline (pre-PD-MCI).

Factors to Consider in Designing Future Trials

The ultimate aim of conducting clinical trials of interventions in PD-MCI is to generate high-quality

evidence that can be used to support treatment decisions in such patients. As outlined in this review, although there has been a good deal of investigation regarding potential treatments, there remains a relative paucity of actionable information for the treatment of PD patients with cognitive disorders. This situation is in part because of the complexity of the problem and the absence of highly targeted interventions, but this outcome is also in part a result of the complexities involved in conducting well-designed trials in this arena. This complexity is further increased when the results of such trials are intended to be used to support applications made to regulatory agencies (eg, Food and Drug Administration, (FDA), European Medicines Agency (EMA)) for marketing approvals. These complexities include the inclusion/exclusion criteria for enrolled patients, the measurement of meaningful outcomes, the time frame of expected therapeutic benefit and study duration, and the utility of biomarkers.

Thanks to the efforts of individual investigators and academic societies (such as the International Parkinson disease and Movement Disorders Society), there is now increased clarity around the diagnostic definitions of specific cognitive syndromes, such as PD-MCI (Movement Disorders Society PD-MCI).⁶ That said, some ambiguities and controversies still remain regarding other cognitive syndromes, including PDD and dementia with Lewy bodies. In addition, particularly for regulatory agencies, there is concern about the differentiation from other cognitive disorders that might exist concomitantly (eg, AD), a concern heightened by the known role of amyloid pathology in PD cognitive disorders. The diagnostic uncertainty may be difficult to resolve, but current definitional advances will assist the acceptance of certain patterns of cognitive dysfunction as intrinsic to the broader PD phenotype. Investigators will need to be clear about which cognitive syndrome they wish to study, as trial designs will accordingly differ. For example, if a trial was designed to slow development of PDD, it may be more pragmatic to enroll PD-MCI patients versus cognitively normal PD, given the event horizon for converting to PDD.

Outcome measures are still in development for PD-MCI, and a broadly accepted, sensitive, reliable, and relevant measure would aid in identifying effective interventions. The only approved drug for PDD (rivastigmine) relied on data from the Alzheimer Disease Assessment Scale–Cognitive Subscale, which was a source of concern at the time of regulatory review, given the AD versus PDD diagnostic uncertainty. Hence, the careful selection of outcome scales will be important not only for identifying therapeutic benefit but also for addressing regulatory concerns about which disease is being studied. In addition, there is

significant precedent within the FDA for requiring both a measure of cognitive performance as well as a measure of functional relevance when assessing drugs for dementia. Recently, the FDA issued guidance about MCI as a result of AD and indicated a single measure that incorporated both aspects (eg, the Clinical Dementia Rating–Sum of Boxes) could be used as the primary outcome in trials to support drug approval.³³ Presumably, the FDA would be open to a similar construct in PD, although such a validated outcome measure for PD does not currently exist. This requirement for a measure of the “functional implication” or “relevance” of a change in cognitive performance significantly complicates the study design of PD-MCI trials. There have been concerns in the AD community that this precedent is onerous and impedes identifying new therapies, but a change in this regulatory position does not appear to be imminent.

Investigators are likely to be interested in both improving cognition in the short term and mitigating long-term decline. These studies would likely use different outcome measures, as some measures are more sensitive to improvement and some are better for capturing decline over time. Scales also have different “ceiling” and “floor” effects and may perform better and worse at different stages of the disease (see previous articles in this miniseries). Careful outcome measure selection should consider the timing and intent of the study intervention. Cognition in PD is also liable to be influenced by multiple factors (eg, mood state, severity of motor parkinsonism, and concomitant medical and surgical therapies), even within a relatively homogeneous category such as PD-MCI, and outcome measure selection should also consider the relative resistance or susceptibility to those effects.

Prior investigations suggest that identifying and quantifying short-term improvement in cognitive performance, along with benefits in a global measure, is reasonably achievable. Such studies are weeks to a few months in duration and tend to involve dozens of research participants. Interventions to improve cognition have immediate and practical effects, and the study designs are not usually complex. This simplicity is aided by the circumstance that cognition does not (aside from placebo effects) typically spontaneously improve in the short term in PD. In contrast, studies that are aimed at improving the chronic decline in cognition are substantially more complex. In this circumstance, the treated and control groups are expected to decline (as opposed to 1 group improving and the other being relatively stable), and the aim is to detect a slowing of that decline in 1 of the groups. Such studies are accordingly longer (to capture the decline) and larger (because the between-group differences may be smaller) and may involve more complicated study designs. The FDA has suggested that

highly relevant milestones (eg, delay in development of dementia) may be applicable in parallel design studies, but studies using clinical outcome measures may need to employ more complex 2-period designs (also called delayed-start designs) to support claims of slowing clinical progression. In that setting, investigators have explored the potential utility of biological measures of disease progression (ie, biomarkers), such as imaging and biofluid indices, to support the clinical observations and to indicate an alteration in the underlying biology of the disease process. Although the biomarker concept is attractive and scientifically adds understanding to the observed effects of interventions, substantial additional work will be needed before such data will support drug approvals. That said, qualified, meaningful biomarkers of the progression of PD cognitive dysfunction would significantly improve the efficiency of clinical trials of interventions designed to slow that process. ■

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