REVIEW

Advances in the Treatment of Cognitive Impairment in Parkinson's Disease

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ABSTRACT: Cognitive impairment in Parkinson's disease (PD) is a frequent complication, with significant interindividual variability in clinical symptoms, severity, timing, and neural substrates. Recent studies have focused not only on understanding PD dementia, but also mild cognitive impairment in PD, which may represent a prodromal stage for dementia. In recent years, there have been important advances regarding clinical characterizations, definitions, associated biomarkers, and risk factors for both mild cognitive impairment in PD and PD dementia. However, there is a paucity of effective therapies for cognitive impairment in PD, whether for mild symptoms or for moderate to severe dementia. At present, only rivastigmine is U.S. Food and Drug Administration approved for PD dementia, an indication received nearly a decade ago. Given the frequency of PD cognitive impairment and its substantial impact on both patients and families, the lack of available and effective treatments represents a striking gap in the field, especially when compared to the large number of available therapies for PD motor symptoms and complications. Improved symptomatic therapies, as well as potential disease-modifying agents, for PD cognitive impairment are needed. Most therapeutic trials for PD dementia and mild cognitive impairment in PD have focused on drugs developed for and tested in Alzheimer's disease, such as cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist, memantine, though recent and ongoing trials examine the effects of pharmacological agents affecting other neurotransmitters, as well as nonpharmacological therapies, including mental and physical exercise and neurostimulation. This review summarizes the design and outcomes of trials for PD cognitive impairment published since 2013 and highlights future therapeutic research opportunities and challenges.

Key Words: cholinesterase inhibitor; clinical trials; dementia; executive function; mild cognitive impairment

Nonmotor symptoms, such as cognitive impairment, in Parkinson's disease (PD) have become increasingly recognized as major contributors to worse patient outcomes, quality of life, disability, and nursing home placement.[1-3] In contrast to the motor symptoms of PD, however, there are few effective, symptomatic treatments for PD cognitive deficits and a paucity of large, randomized, double-blind, placebo-controlled trials for PD dementia (PDD) or mild cognitive impairment in PD (PD-MCI). To date, there are no therapeutic interventions known to slow down or halt cognitive decline in PD. The sole medication approved by the U.S. Food and Drug Administration (FDA) for PDD, rivastigmine, received this indication almost a decade ago.[4] Although there is strong evidence for cholinergic dysfunction in PD cognitive impairment, supporting the use of cholinesterase inhibitors in this population, the important point is that all existing symptomatic therapeutics for PDD and PD-MCI were originally tested and approved for use in Alzheimer's disease (AD).[5,6]

Recent years have seen advances in our clinical and biomarker characterizations of PDD and PD-MCI, as

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well as our understanding of their different cognitive phenotypes and rates of progression. Increasing numbers of clinical trials are focused on symptomatic treatments for PD cognition, including novel agents and nonpharmacological interventions. Diagnostic criteria for PDD and PD-MCI have been published by International Parkinson and Movement Disorder Society (MDS) Task Forces, aim to capture the unique cognitive and behavioral deficits of PD, and provide uniform criteria for enrollment of PDD and PD-MCI patients into clinical trials.[7,8] Though several validated, PD-specific cognitive scales have been developed, further study is needed to determine the optimal cognitive tests or batteries to be used as clinical trial outcome measures.[9,10] In this article, we summarize the study design features and outcomes of clinical research trials in cohorts of PDD and PD-MCI patients published since 2013, with an emphasis on randomized trials. We also describe several trials in patients with dementia with Lewy bodies (DLB), owing to the fact that several trials combined PDD and DLB patients. Lastly, we discuss several challenges and priority areas of future therapeutic research in PD cognitive impairment.

New Treatments and Discoveries

PDD and DLB

Clinical trials in PDD, and in some cases, combined with DLB, have investigated cholinesterase inhibitors and memantine as part of randomized, double-blind, placebo-controlled studies, open-label extensions, or other study mechanisms. More recently, novel agents invoking the serotonergic and other neurotransmitter systems are being studied. In addition, nonpharmacological interventions, such as deep brain stimulation (DBS), are being explored for PDD and DLB.

Pharmacological Interventions

This section will highlight clinical trials with medication interventions, including completed and ongoing studies (Tables 1 and 2, respectively).

PDD

Since 2013, there have been no new publications reporting on randomized, double-blind, placebo-controlled studies exclusively for PDD patients. Other studies on therapeutic interventions for PDD published between 2013 and 2015 include an open-label, long-term safety study of rivastigmine[11] and an exploratory study of rivastigmine's effect on brain activity.[12] Emre and colleagues examined the long-term safety of rivastigmine in 583 PDD subjects randomized to either oral or transdermal formulation in a 76-week, multicenter, open-label study.[11] Primary outcome measures were the incidence of worsened motor function or discontinuation rate owing to predefined potential adverse effects (AEs) of rivastigmine capsules; secondary outcomes included AEs with the patch, along with other efficacy measures, such as the Mattis Dementia Rating Scale (DRS), AD Cooperative Study-Activities of Daily Living (ADCS-ADL) scale, and Neuropsychiatric Inventory (NPI-10). The incidence of AEs owing to worsened motor symptoms or discontinuation was similar regardless of formulation, though more tremor was reported in the capsule group. There was significant efficacy in favor of the capsules on the DRS, NPI-10, and ADCS-ADL at week 76, compared with earlier time points; however, in PDD subjects with Mini–Mental State Examination (MMSE) scores >21, there were no differences in DRS or ADCS-ADL scores. This study supports the long-term safety of rivastigmine in PDD.

Given the proposed benefit of cholinesterase inhibitors on attention and executive function in PD, another study investigated the effect of rivastigmine treatment on spontaneous brain activity measured by low-frequency fluctuations in resting-state functional MRI (fMRI).[12] Twelve subjects (6 PDD, 6 PD-MCI) were studied at baseline and then at 12 weeks after dose escalation to rivastigmine 9.5 mg/24-hour patch. Compared to healthy controls, PD subjects had reduced brain activity in frontal regions, hippocampus, precuneus, and angular gyrus at baseline and post-treatment; however, other regions, such as the right caudate and left thalamus, had decreased frequency fluctuations after treatment. By masking regions where PD subjects had abnormally low frequencies and comparing voxel-wise differences across the two time points, there was increased brain activity in the left precentral gyrus/inferior frontal gyrus pars opercularis and left supplementary area after treatment. Although further study is needed, these results suggest that cognitive enhancing medications may exert pathophysiological influences on brain activity.

Of the currently listed www.clinicaltrials.gov open studies for PDD, only one is a randomized, double-blind, placebo-controlled medication study in PDD. This trial, called SYNAPSE, is a randomized, double-blind, placebo-controlled, proof-of-concept, phase II study to evaluate the safety, tolerability, and efficacy of SYN120, a dual 5-HT6/5-HT2A antagonist, in PDD patients already treated with a stable dose of cholinesterase inhibitor (NCT02258152, www.clinicaltrials.gov). SYN120 is a novel compound that expands the field of cognitive enhancing drugs beyond those affecting the cholinergic (i.e., cholinesterase inhibitors) and glutamatergic (i.e., memantine) systems to include the serotonin system. Both 5-HT6 and 5-HT2A receptors are widely distributed in brain regions highly implicated in cognitive processes, psychosis, and mood, including the prefrontal cortex and hippocampus.[13,14] Whereas many antipsychotics act on 5-HT2A receptors, the

TABLE 1. Clinical trials in PDD alone and in combination with DLB (2013–2015)

Study	Compound	Mechanism of Action	Trial Design (AAN Class of Evidence)	Diagnosis	Patients (n)	Follow-up Period	Outcome Measure(s)	Results
Emre et al., 2014	Rivastigmine, 12 mg oral capsules daily vs. 9.5 mg/24-hour patch daily	Cholinesterase inhibition	Randomized, multicenter, open-label study (Class III)	PDD (defined by DSM-IV and MMSE 10–26)	Screened for eligibility: 738 Randomized: 583 Study completers: 359	76 weeks	Primary: Incidence of, discontinuation to, AEs (motor worsening with capsules) Secondary: Frequency of AEs/serious AEs Efficacy: ADCS-ADL, NPI-10, MDRS	No difference in predefined AEs or discontinuation because of motor symptoms with either rivastigmine forumulation; significant efficacy favoring capsules on MDRS, NPI-10, ADCS-ADL (subjects with MMSE >21: no differences in MDRS or ADCS-ADL)
Stubendorff et al., 2014	Memantine, 20 mg daily	NMDA receptor antagonist	Open-label extension of randomized, double-blind, placebo-controlled trial by Aarsland et al., 2009 (Class III)	PDD (defined by DSM-IV, MMSE ≥12) or DLB (defined by McKeith criteria, MMSE ≥12)	Initial study: 72 Screened for eligibility: 42 (from Swedish group) Followed: 32 (16 PDD, 16 DLB) Study completers: 17	36 months	Primary: Survival	15 of 32 (47%) died during follow-up;memantine group had longer survival compared to placebo group; memantine responders had higher survival rates compared to nonresponders
Wesnes et al., 2015	Memantine, 20 mg daily	NMDA receptor antagonist	Post-hoc analysis of randomized, double-blind, placebo-controlled trial by Aarsland et al., 2009 (Class II)	PDD (defined by DSM-IV, MMSE ≥12) or DLB (defined by McKeith criteria, MMSE ≥12)	Initial study: 72 Screened for eligibility: 59 Followed: 51 (30 PDD, 21 DLB) Study completers: 48	24 weeks	Primary: CDR System tests of attention (simple and choice reaction time) and word recognition (immediate and delayed)	Improvement in choice reaction time, immediate and delayed word recognition in memantine group; no significant difference for simple reaction time test
Ikeda et al., 2013 (on behalf of Donepezil-DLB Study Investigators)	Donepezil, 5 mg daily	Cholinesterase inhibition	Open-label extension of randomized, double-blind, placebo-controlled trial by Mori et al., 2012 (Class III)	DLB (defined by McKeith criteria, MMSE 10–26)	Initial study: 123 Screened for eligibility: 113 Followed: 108 Study completers: 81	52 weeks	Primary: MMSE, NPI, CFI, Zarit Caregiver Burden Interview Secondary: AEs	Improvement in cognitive function, behavioral symptoms, cognitive fluctuations maintained after 52

(Continued)

TABLE 1. *Continued*

Study	Compound	Mechanism of Action	Trial Design (AAN Class of Evidence)	Diagnosis	Patients (n)	Follow-up Period	Outcome Measure(s)	Results
								weeks; caregiver burden was reduced at 52 weeks; no significant difference in AEs across groups by onset time, no significant delayed AEs
Ikeda et al., 2015	Donepezil, 5 mg daily vs. 10 mg daily	Cholinesterase inhibition	Randomized, placebo-controlled, double-blind trial, phase III (Class II)	DLB (defined by McKeith criteria, MMSE 10–26, Clinical Dementia Rating $\geq$0.5)	Screened for eligibility: 161 Randomized: 142 Study completers: 111	12 weeks	Co-Primary: MMSE and NPI-2 (hallucinations and fluctuations scores) Secondary: Zarit Caregiver Burden Interview, AEs	No significant superiority of either donepezil group vs. placebo, though for MMSE alone, statistically significant differences for donepezil 10 mg daily vs. placebo; no significant improvement in caregiver burden score; no significant difference in AEs
Mori et al., 2015	Donepezil, 10 mg daily	Cholinesterase inhibition	Open-label extension of randomized, placebo-controlled, double-blind trial, by Ikeda et al., 2015 (Class III)	DLB (defined by McKeith criteria, MMSE 10–26, Clinical Dementia Rating $\geq$0.5)	Initial study: 142 Screened for eligibility: 110 Followed: 110 Study completers: 100	36 weeks	Primary: MMSE, NPI-2, NPI-10, Caregiver Burden Interview, AEs	Modest improvements in MMSE, NPI-2, NPI-10 scores sustained at end of OLE; no significant difference in AEs or delayed onset of AEs

CFI, Cognitive Fluctuations Inventory; GDS, Geriatric Depression Scale; NMDA, N-methyl-D-aspartate; OLE, Open-label extension; PD-Q, PD Questionnaire.

5-HT6 receptor has potential as a target for cognitive impairment, given its pharmacology, localization, preclinical evidence, and animal studies.[15-17] The SYNAPSE study defines PDD using MDS Task Force criteria and a Montreal Cognitive Assessment (MoCA) score of 10 to 23, in contrast to preceding randomized, controlled trials (e.g., rivastigmine and donepezil), which defined PDD using Diagnostic and Statistical Manual of Mentla Disorders, Fourth Edition (DSM-IV) criteria and MMSE scores ranging from 10 to 26.[4,18-24] Unlike the DSM-IV criteria, the MDS PDD criteria do not require that memory be one of the cognitive domains impaired. This may be an important factor when evaluating different drug compounds for PD cognitive impairment (i.e., some drugs may preferentially target memory, or executive function, or attention) given the known heterogeneity of PDD, both clinically (e.g., greater executive dysfunction or greater memory impairment in some patients) and pathologically (e.g., comorbid AD-type pathology in approximately one third of PDD patients at autopsy).[7,25,26] Furthermore, the MMSE, though an easily administered screening tool, does not adequately assess executive function or detect cognitive impairment in PD, whereas other tests, such as the MoCA, may have better screening properties in PD.[27-29] In addition, the primary outcome measure is the change in Cognitive Drug Research (CDR) Computerized Cognition Battery Continuity of Attention. Although the CDR system has been used in DLB and other PD trials and as a secondary endpoint in the rivastigmine EXPRESS trial,[30,31] most preceding PDD randomized, controlled trials (e.g., rivastigmine, donepezil, and memantine) had primary outcome measures drawn from the AD field, utilizing the ADAS-Cog alone,[24] ADCS-CGIC alone,[21] ADAS-Cog along with either the ADCS-Clinician's Global Impression of Change (CGIC) [4] or Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+),[20] MMSE along with the CIBIC+,[19] or DRS,[22,23] or CGIC alone.[18]

The www.clinicaltrials.gov website also cites two studies of donepezil in PDD. In a 24-week study, a Korean group will compare high-dose donepezil 23 mg daily to 10 mg daily in PDD patients with MMSE 10 to 24 (NCT02415062); the Korean MMSE-2 is the primary outcome measure, with secondary outcomes including cognitive, motor, and ADL scales. Although the donepezil 23-mg dose is FDA approved for moderate to severe AD,[32] this higher dose has not been systematically studied in PD. The MUSTARDD-PD study was a large phase III trial of donepezil compared to placebo in mild PDD and PD-MCI subjects recruited across 22 sites in the United Kingdom (NCT01014858), but was stopped prematurely owing to poor enrollment, highlighting the challenges in conducting large-scale clinical trials for PDD; this trial also included a Scales Assessment Study to examine which cognitive scales are best to monitor cognitive performance over time and response to drug interventions. No results have been reported.

PDD and DLB Combined

Although whether or not PDD and DLB are separate entities remains a debated topic, several studies, including two randomized, double-blind, placebo-controlled trials with memantine, have combined PDD and DLB participants into a single Lewy body disease (LBD) group.[18,21] Merits of this, however, can be argued, given that clinical and pathological differences could influence treatment response and AEs. In recent years, several trials combined PDD and DLB cohorts, with two studies generating open-label follow-up data or secondary analyses from the randomized, controlled memantine trial by Aarsland and colleagues.[18] Stubendorff and colleagues report long-term follow-up and survival data on the 32 Swedish PDD and DLB subjects enrolled in the initial study who were subsequently treated with open-label memantine 20 mg daily and followed with annual clinic visits.[33] Survival was assessed at 36 months from baseline, comparing the initially assigned memantine and placebo groups and also responders and nonresponders, defined by CGIC scores reflecting improvement versus worsening, in the memantine and placebo groups. During follow-up, 15 of 32 (47%) participants died; there were significantly more deaths in the placebo group, compared to memantine-treated group, and in nonresponders compared to responders. Also drawing from the memantine trial by Aarsland and colleagues,[18] Wesnes and colleagues analyzed data from the CDR System tests of attention (simple and choice reaction time) and word recognition (immediate and delayed) at baseline, 12 weeks, and 24 weeks in 51 PDD and DLB subjects.[34] Compared to placebo, memantine improved scores on choice reaction time and immediate and delayed word recognition, but not on simple reaction time test. There were significant correlations between several CDR tests and MMSE, Disability Assessment for Dementia scale, and quality-of-life ratings; choice reaction time test speed declined in those with ADCS-CGIC scores denoting worsening.

The www.clinicaltrials.gov website lists an open-label study investigating the effect of armodafinil on attentional impairment in PDD and DLB, as evidenced by changes in striatal-thalamo-cortical network activity measured with EEG frequency analysis (NCT01256905). Armodafinil, an agent similar to modafinil, promotes wakefulness through unknown mechanisms and is used to treat excessive daytime sleepiness associated with obstructive sleep apnea, narcolepsy, and shift work disorder. To date, no results are available.

DLB Alone

Three recent studies investigated donepezil in DLB alone, with two studies providing long-term follow-up

TABLE 2. Unpublished and ongoing clinical trials in PDD and DLB

Study Identifier	Compound/ Intervention	Mechanism of Action	Trial Design	Diagnosis	Patients (n)	Follow-up Period	Type of Study	Outcome Measure(s)	Status
NCT02258152	SYN120, added to stable cholinesterase inhibitor	Dual 5-HT6/5-HT2A antagonist	Randomized, double-blind, placebo-controlled trial, phase II	PDD (defined by MDS criteria and MoCA 10–23)	80	16 weeks	Symptomatic	Primary: change in CDR Computerized Cognition Battery Continuity of Attention	Recruiting
NCT02415062	Donepezil, 23 mg daily vs. 10 mg daily	Cholinesterase inhibition	Randomized, parallel, open-label trial, phase II	PDD (defined by MMSE 10–24)	150	24 weeks	Symptomatic	Primary: Korean MMSE-2, Secondary: Korean-IADL, Clinical Dementia Rating scales ADL, UPDRS part 3, Modified H & Y, Schwab & England ADLs, NPI, Global Deterioration Scale, Korean MoCA, Semantic fluency	Not yet recruiting
NCT01256905	Armodafinil, 150 mg daily	Wakefulness-promoting agent	Open-label study	PDD (defined by MDS criteria), DLB (defined by McKeith criteria); both with MMSE <24 and/or DRS-2 score <134, CAF >4)	20	2 hours	Symptomatic	Primary: EEG frequency analysis, attentional modulation	Unknown (last verified 2010), no published results
NCT01701544	DBS, Bilateral nucleus basalis of Meynert	Neurosurgical	Randomized, double-blind, cross-over, controlled trial	PDD (defined by MMSE 21–26)	6	3 months (on), 3 months (off)	Symptomatic	Primary: Abbreviated cognitive battery, CVLT-II, Verbal fluency, Simple and choice reaction time task, WAIS-IV Digit Span, Posner's Covert (all *on* vs. *off*), Secondary: MMSE, DRS-2, WASI, Short Recognition Memory, WAIS-IV Letter Number Sequencing, NPI, Florida Apraxia Screening test, CGI, Hamilton Depression Scale, Blessed Dementia Scale, MDS-UPDRS, Gait and falls questionnaire, NMS Quest, PDQ-39 (all *on* vs. *off*)	Recruiting by invitation
NCT02263937	DBS, Bilateral nucleus basalis of Meynert	Neurosurgical	Randomized, double-blind, cross-over, controlled trial	DLB (defined by McKeith criteria)	6	6 weeks, 14 weeks	Symptomatic	Primary: HVLT, Verbal fluency, Simple and choice reaction time task, WAIS-IV Digit Span, Posner's Covert Attention test, CAF (all *on* vs. *off*)	Recruiting

(Continued)

TABLE 2. *Continued*

Study Identifier	Compound/ Intervention	Mechanism of Action	Trial Design	Diagnosis	Patients (n)	Follow-up Period	Type of Study	Outcome Measure(s)	Status
								Secondary: MMSE, DRS-2, WASI, Short Recognition Memory, WAIS-IV Letter Number Sequencing, TMT, Stroop, WAIS-IV Symbol search, JLO, NEVHI, NPI, Florida Apraxia Screening test, CGI, Hamilton Depression Scale, Hamilton Anxiety Scale, Starkstein Apathy Rating Scale, MDS-UPDRS, FOG questionnaire, SCOPA-AUT, QoL-AD, Mayo Fluctuations Composite Scale, Blessed Dementia Scale, Carer Strain Index, Short Form 36 (all *on* vs. *off*)	
MUSTARDD-PD, NCT01014858	Donepezil, 10 mg daily	Cholinesterase inhibition	Randomized, double-blind, controlled multicenter trial, phase III (Class I)	PDD (mild, defined by MDS criteria and ACE-R of $\leq$88 and DRS-2 of 5–8)	500	24 months	Symptomatic	Primary: cognitive function, neuropsychiatric burden, functional ability Secondary: patient and carer quality of life, cost-effectiveness; scales substudy comparing response of scales over time and with drug intervention	Suspended, no results yet

ACE-R, Addenbrooke's Cognitive Examination; CAF, Clinical Assessment of Fluctuation; CGI, Clinical Global Impression Scale; FOG, freezing of gait; HVLT, Hopkins Verbal Learning Test; IADL, Instrumental ADL; JLO, Judgment of Line Orientation; NMS Quest, Nonmotor Symptoms Questionnaire; NEVHI, North East Visual Hallucinations Interview; QoL, Quality of life; SCOPA-AUT, Scales for Outcome in Parkinson's Disease–Autonomic; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

data in open-label extension study phases and one randomized, placebo-controlled, phase III trial.[35-37] On behalf of the Donepezil-DLB Study Investigators in Japan, Ikeda and colleagues reported long-term safety and efficacy data of donepezil 5 mg daily after a 52-week, open-label, multicenter extension study.[35,38] Modest, but statistically significant, improvement in MMSE, NPI, and fluctuations in cognition (measured by Cognitive Fluctuation Inventory) occurred after donepezil treatment and was maintained for 52 weeks, compared to baseline. However, caregiver burden, though improved in the preceding randomized, controlled trial, increased at the 52-week time point. In a randomized, controlled trial, Ikeda and colleagues examined the superiority of donepezil (5 or 10 mg daily) to placebo after 12 weeks in 142 DLB subjects.[37] The coprimary endpoints were change in cognitive function measured by the MMSE and NPI-2 (sum of hallucinations and cognitive fluctuations scores). Study results did not confirm the predefined superiority of either donepezil group compared to placebo for the coprimary endpoints, though examining the MMSE independently for the donepezil 10 mg daily versus placebo group revealed a modest, but statistically significant, change. Mori and colleagues reported the long-term efficacy and safety data of the DLB subjects from the previously discussed randomized, controlled trial (Ikeda and colleagues, 2015) after a 36-week open-label extension phase and treatment with donepezil 10 mg daily.[36,37] Modest improvement in MMSE and NPI-2 scores were sustained at the end of the open-label period. Approximately 20% of the cohort required dose reduction after week 24 primarily owing to gastrointestinal, psychiatric, and parkinsonian symptoms, though most treatment-related AEs were mild or moderate.

Nonpharmacological Interventions in PDD and DLB

From the www.clinicaltrials.gov website are two ongoing studies of DBS in PDD and DLB subjects targeting the bilateral nucleus basalis of Meynert, a cholinergic-innervated basal forebrain site involved in attention, learning, and memory processes and impaired in AD and dementia. The nucleus basalis of Meynert has been a surgical target in pilot studies of AD and in case reports of PDD patients demonstrating improved cognitive function and apraxia.[39-41] The PDD randomized, double-blind study involves a crossover design of stimulation (i.e., *on-off* or *off-on*) in 6 patients with motor fluctuations and dementia (MMSE 21–26; NCT01701544), and the DLB study uses a similar crossover design (NCT02263937). For both trials, DBS electrodes will be placed in nucleus basalis of Meynert and globus pallidus interna with an option for stimulating the latter site after crossover.

PD-MCI or Nondemented but Cognitively Impaired PD

In recent years, therapeutic trials have expanded beyond PDD to focus on cognitive deficits in nondemented PD patients. These trials include pharmacological agents targeting the cholinergic, dopaminergic, and noradrenergic systems, as well as nonpharmacological interventions, such as cognitive training, physical exercise, and transcranial stimulation.

Pharmacological Interventions

This section will highlight clinical trials with pharmacological agents, such as cholinesterase inhibitors, monoamine oxidase B (MAO-B) inhibitors, and atomoxetine, including completed and ongoing studies (Tables 3 and 4, respectively).

Cholinergic System

There is good rationale for the study of cholinesterase inhibitors in nondemented PD patients with cognitive deficits, given evidence of cholinergic dysfunction in PD cognitive impairment and cholinesterase inhibitor use in PDD, DLB, and AD. To date, however, few randomized, controlled trials with cholinesterase inhibitors have been completed or published in PD with mild cognitive dysfunction. A recently published trial reports on a 24-week, randomized, double-blind, placebo-controlled, crossover, single-site study of the rivastigmine patch (target dose: 9.5 mg/24 hour) in 28 PD-MCI subjects meeting Winblad criteria for MCI, Clinical Dementia Rating score of 0.5, and MDRS-2 scaled score less than 8 (i.e., <25th percentile).[8,42] The primary outcome measure was the ADCS-CGIC for MCI score,[43] with secondary outcome measures including other tests for cognition (e.g., NeuroTrax computerized testing),[44] instrumental ADLs, psychiatric features, and motor function. There was no significant difference between rivastigmine and placebo groups in ADCS-CGIC scores ($P = 0.096$), though there was a significant effect on the Everyday Cognition Battery ($P = 0.03$), a performance-based measure of instrumental ADLs.[45] Treatment adherence was high in both groups, with no significant differences in AEs; rash and increased *off* time were more common in the rivastigmine-treated group, and worsened cognition, increased depression, and weight loss were more common in the placebo group. Although cognitive effects were negative, this study represents a first step in symptomatic, randomized, controlled trials for PD-MCI. Future studies with larger sample sizes and more powerful study designs may be informative.

An upcoming PD-MCI study will compare donepezil to a "no-intervention" control group, recruiting 80 PD-MCI subjects, designated by MDS Task Force

TABLE 3. Clinical trials in nondemented PD subjects with cognitive impairment (2013–2015)

Study	Compound	Mechanism of Action	Trial design (AAN Class of Evidence)	Diagnosis	Patients (n)	Follow-up Period	Outcome Measure(s)	Results
Mamikonyan et al., 2015	Rivastigmine, 9.5 mg/24-hour patch daily	Cholinsterase inhibition	Randomized placebo-controlled, double-blind, cross-over trial (Class I)	PD-MCI (defined by Winblad criteria, Clinical Dementia Rating score = 0.5, MDRS-2 <8)	Screened for eligibility: 48 Followed: 28 Study completers: 23	24 weeks	Primary: ADCS-CGIC for MCI Secondary: NeuroTrax computerized cognitive testing, MoCA, MDRS-2, attention tests, ADLs (Everyday Cognition Battery, Penn Daily Activities Questionnaire), Psychiatric features (GDS-15, Parkinson's Psychosis Scale, Apathy Scale), UPDRS Part 3, PDQ-8	No significant differences between groups for primary outcome; significant difference on the exploratory outcome Everyday Cognition Battery
Frakey and Friedman, 2014	Rasgailine, 1 mg daily	MAO-B inhibition	Randomized, double-blind, placebo-controlled trial, phase IV (Class I ? [limited information])	PD with MMSE >23 and nondepressed (Beck Depression Inventory short form <8)	Screened for eligibility: unknown Followed: 50 Study completers: 45	24 weeks	Primary: Rey Auditory Verbal Learning test Secondary: COWAT, Animal fluency, JLO, WAIS-IV Digit Span, TMT, Digit Symbol Modalities Test, PDQ-39	No significant differences between groups on cognitive or neuropsychological measures; rasagiline group had improved motor symptoms

COWAT, Controlled Oral Word Association Test; GDS, Geriatric Depression Scale; JLO, Judgment of Line Orientation; PD-Q, PD Questionnaire.

TABLE 4. Unpublished and ongoing clinical trials in nondemented PD subjects with cognitive impairment

Study Identifier	Compound / Intervention	Mechanism of Action	Trial Design	Diagnosis	Patients (n)	Follow-up Period	Type of Study	Outcome Measure(s)	Status
NCT02450786	Donepezil, 10 mg daily	Cholinesterase inhibition	Randomized, parallel, open-label trial (donepezil vs. control group), phase II	PD-MCI (defined by MDS criteria)	80	48 weeks	Symptomatic	Primary: Korean MMSE Secondary: Changes in cognitive decline, PD motor scale, UPDRS 1 to 4, structural and functional brain MRI, functional brain connectivity, Seoul Neuropsychological Screening Battery	Not yet recruiting
NCT01497652	Rasagiline, 1 mg daily	MAO-B inhibition	Randomized, double-blind, placebo-controlled trial, phase IV	PD-MCI (defined as MoCA 22–27), GDS <5	40	14 weeks	Symptomatic	Primary: MoCA Secondary: SCOPA-COG, FAB, UPDRS 2 and 3	Completed, no published results
MODERATO, NCT01723228	Rasagiline, 1 mg daily	MAO-B inhibition	Randomized, double-blind, placebo-controlled multicenter trial, phase IV	PD-MCI (defined by MDS criteria and MoCA 20–25)	170	24 weeks	Symptomatic	Primary: SCOPA-COG Secondary: UPDRS part 2 and 3, MoCA, ADCS MCI-CGIC	Completed, no published results
NCT01738191	Atomoxetine, 80 mg daily	Norepinephrine reuptake inhibitor	Randomized, double-blind, placebo-controlled trial, phase II	PD-MCI (defined by MDS criteria and MoCA 21–25)	30	12 weeks	Symptomatic	Primary: Global treatment effect of neuropsychological testing battery Secondary: Safety, UPDRS, AEs Other: MoCA, UPDRS, PDQ-39, GDS, GAI	Completed, no published results
NCT01340885	Atomoxetine, 20 to 60 mg daily, rivastigmine 3 to 9 mg daily	Norepinephrine reuptake inhibitor, cholinesterase inhibition	Randomized, double-blind, placebo-controlled trial, phase IV	PD without dementia	50	6 weeks	Symptomatic	Primary: Attention network effects Secondary: PDQ-39, Stroop Color Word Test, Fatigue, Depression, Daytime Sleepiness	Unknown (last verified 2012), no published results
NCT02225314	Brain Fitness vs. InSight programs vs. active control	Behavioral interventions	Randomized, open label	PD-MCI (defined by MDS criteria)	30	3 months	Symptomatic	Primary: Percent accuracy on cognitive training quizzes Secondary: PDQ-39, CVLT-II Long Delay Free Recall Scaled Score	Recruiting

(Continued)

TABLE 4. *Continued*

Study Identifier	Compound / Intervention	Mechanism of Action	Trial Design	Diagnosis	Patients (n)	Follow-up Period	Type of Study	Outcome Measure(s)	Status
NCT02048605	Psychosocial cognitive-behavioral therapy-based training vs. unspecific group training	Behavioral interventions	Randomized, double-blind, controlled trial	PD, either cognitively normal, MCI, or mild dementia (MMSE $\geq$24)	40	6 months	Symptomatic	Primary: SeiQol-DW Secondary: Scale for the Assessment of Management of Daily Living, Burden Questionnaire, Psychosocial Problems Questionnaire	Recruiting
NCT02267785	Skill-based exercise vs. aerobic exercise vs. social contact	Exercise	Randomized, single-blind, controlled trial	PD-MCI (defined by MDS criteria)	150	12 weeks	Symptomatic	Primary: Executive function (WCST, verbal fluency, Adaptive Digit Ordering Test-A), Context Dependent Motor Learning, fMRI task Secondary: PDQ-39, MDS-UPDRS part 3, exercise scales (ABC, CONF, BEL, EFFIC), FrSBe, Motor Skill Fitness, Cardiovascular Fitness	Recruiting
NCT01156714	Exercise and cognitive training (treadmill vs. computerized memory testing vs. combination)	Exercise/behavioral interventions	Randomized, single-blind, controlled trial	PD with balance problems	121	3 months	Symptomatic	Primary: dual task ability, executive function, instrumental activities of daily living Secondary: dual task ability, instrumental activities of daily living	Recruiting
NCT02346708	Real vs. sham TMS	Neuromodulation	Randomized, double-blind, controlled trial	PD with MCI	150	2 weeks	Symptomatic	Primary: MEG connectivity Secondary: cognitive scores, MDRS; TMT-B, verbal fluency, Stroop; HVLT; BNT; BTA; JLO	Recruiting

ABC, Activity Specific Balance Confidence; BEL, Exercise Control Beliefs; BNT, Boston Naming Test; BTA, Brief Test of Attention; CONF, Confidence in ability to maintain exercise program; EFFIC, Self-efficacy for Exercise Scale; FrSBe, Frontal Systems Behavior scale; GAI, Geriatric Anxiety scale; HVLT, Hopkins Verbal Learning Test, JLO, Judgment of Line Orientation; PD-Q, PD Questionnaire; SeiQol-DW, Schedule for the Evaluation of Individual Quality of Life-Direct Weighting; WCST, Wisconsin Card Sorting Test.

criteria. The primary outcome measure is the rate of cognitive decline as measured by the Korean MMSE at 48 weeks, with secondary outcomes measuring changes in cognition, motor function, and structural and functional connectivity on neuroimaging (NCT02450786).

Dopaminergic System

Based on promising findings from an earlier trial of rasagiline, a MAO-B inhibitor, in PD-MCI,[46] three other randomized, double-blind, placebo-controlled studies of rasagiline for PD cognitive deficits have been completed. Frakey and Freidman studied 50 PD nondepressed subjects with MMSE scores >23 in a 6-month, double-blind, placebo-controlled, single-site trial with rasagiline 1 mg daily (NCT01382342). The primary outcome measure was the change in the Rey Auditory Verbal Learning Test scores, whereas secondary outcome measures included tests for verbal fluency, attention, executive function, and language abilities. As reported in the abstract, there were no significant differences between the rasagiline and placebo groups on cognitive variables.[47] Another randomized, double-blind, placebo-controlled, single-site PD trial with rasagiline 1 mg daily for 12 weeks examined whether rasgaline improved MoCA scores, with secondary objectives assessing change in other cognitive, frontal lobe/executive function, motor, and ADL scales (NCT01497652). No results have been reported. Recently, a large multicenter, randomized, double-blind, placebo-controlled, 24-week trial of rasagiline 1 mg daily versus placebo has been completed in PD-MCI subjects, defined by the MDS criteria and MoCA scores 20 to 25 (NCT01723228). The primary endpoint was the mean change in Scales for Outcomes in Parkinson's disease-Cognition (SCOPA-COG) summary score and secondary outcome measures for motor, ADL, functional independence, and MoCA scores. No results except for baseline data are reported to date.[48] Another MAO-B inhibitor, safinamide, was studied in an earlier, randomized, double-blind, placebo-controlled, multicenter study in nondemented PD subjects with cognitive impairment using the PD Cognitive Rating Scale (NCT01211587), though no results have been published.

Noradrenergic System

Atomoxetine, a norepinephrine reuptake inhibitor indicated for attention deficit hyperactivity disorder, has been suggested to improve PD cognitive deficits.[49,50] A randomized, double-blind, placebo-controlled, single-site, 12-week study of atomoxetine (up to 80 mg daily) in 30 PD-MCI subjects with MoCA scores 21 to 25 has been completed, though no results are available yet (NCT01738191). The primary outcome measure for this study was the global treatment effect based on a neuropsychological test battery. Another trial listed in the ClinicalTrials.gov website is a 6-week, randomized, double-blind, placebo-controlled, single-site trial comparing atomoxetine (20–60 mg daily), rivastigmine (3–9 mg daily), or placebo and cognitive decline in nondemented PD, with outcomes focused on attention network effects, quality of life, Stroop Color Word Test, and nonmotor symptoms (fatigue, depression, and daytime sleepiness; NCT01340885). No results have been reported.

Nonpharmacological Interventions

Nonpharmacological strategies for treating PD cognitive impairment represent an area of growing interest and include cognitive training, physical exercise and physical therapy, music and art therapy, and noninvasive brain stimulation techniques.[51-53] To date, many studies are open-label pilot studies; though there are several small, randomized, controlled trials, "double-blinding" of study personnel and patients in these types of interventions can be challenging. There is great heterogeneity in study methodologies (e.g., different types of cognitive tasks and means of assessments [computerized interventions, neuropsychological tests, word games, along with duration of study and practice], physical exercises and methods [aerobic, dance, strength, and so on], and cognitive targets [attention, executive function, memory, and so on]). Studies in PD have generally focused on cognitively intact or nondemented, but mildly cognitively impaired, PD patients, rather than those with PDD, though nonpharmacological approaches have been studied in AD (Table 5).[54-56]

Cognitive Therapies

A variety of interventions have been studied, ranging from cognitive training exercises, computerized brain training, to nonphysical leisure activities. Besides potentially improving cognitive outcomes, these interventions may have positive effects on instrumental ADLs, such as driving, and safety. Edwards and colleagues conducted a randomized, single-blind, single-site, controlled trial of cognitive speed of processing training in PD patients using a commercially available, self-administered computer program (InSight software).[57] In this study, 87 cognitively intact PD patients were randomized to either 20 hours of self-administered cognitive speed of processing training or a no-contact control condition for 3 months. The primary outcome measure was the useful field-of-view test performance, a computer-administered test of processing speed with increasingly cognitively demanding visual attention tasks that simulates aspects of driving, and secondary outcomes of cognitive self-perceptions and depressive symptoms. Findings revealed an 85% completion rate, feasibility of subject's administering the speed of processing training modules, and an improvement in speed of processing in the active treatment group, though also, to some degree, in the control group. Peña and colleagues conducted a randomized, single-blind, single-site, controlled trial of

TABLE 5. Clinical trials assessing cognition in PD subjects without cognitive impairment (2013–2015)

Study	Compound	Mechanism of Action	Trial Design (AAN Class of Evidence)	Diagnosis	Patients (n)	Follow-up Period	Outcome Measure(s)	Results
Edwards et al., 2013	Cognitive speed of processing training vs. noncontact control condition	Cognitive training	Randomized, single-blind, controlled trial (Class III—per article)	PD without dementia, MMSE $\geq$24	Screened for eligibility: 93 Followed: 87 Study completers: 74	3 months	Primary: useful field of view test, Secondary: finger tapping task, self-rated health, MoCA, UPDRS, Cognitive Self-Report Questionnaire, CES-D	Significant improvement in speed of processing in active treatment group compared to controls; no significant differences on secondary outcomes
Peña et al., 2014	REHACOP vs. control group (occupational activities)	Cognitive training	Randomized, single-blind, controlled trial (Class II—per article)	PD without dementia	Screened for eligibility: 50 Followed: 44 Study completers: 42	3 months	Primary: Processing speed (TMT-A, Salthouse Letter comparison), verbal memory (HVLT), visual memory (BVMT), executive function (Stroop), TOM (Happé) scores Secondary: NPI-Q, GDS, Lille Apathy scale, WHO-DAS II	Significant improvement in processing speed, visual memory, theory of mid, functional disability in REHACOP group compared to controls; significant improvement on TOM and functional disability
Cerasa et al., 2014	Computer-based attention training (Rehacom) vs. control group (computerized tapping task)	Cognitive training	Randomized, single-blind, controlled trial (Class III)	PD without dementia, but having deficits in either attention and/or information processing speed, working memory, and/or executive functioning	Screened for eligibility: 137 Followed: 20 Study completers: 15	6 weeks	Primary: neuropsychological test battery (ROCFT, SRT, JLO, COWAT, SDMT, PASAT, Digit Span, Stroop, TMTA-B Secondary: State-trait anxiety inventory, PDQ-39 Other: resting state fMRI	Significant improvement in SDMT and Digit Span forward tests in experimental group compared to control group; changes in fMRI left-sided attention and central executive networks
McKee and Hackney, 2013	Tango vs. education lessons	Exercise	Randomized, single-blind, controlled trial (Class II?)	PD patients	Screened for eligibility: unknown Followed: 33 Study completers: 31	1 week, 10 to 12 weeks	Primary: MoCA, Reverse Corsi Blacks, Brooks Spatial Task;disease/motor measures (UPDRS part 3, Fullerton Advanced Balance Scale, Four-Square	Significant improvements in spatial cognition, executive function, disease severity, and balance in tango group compared to education group;

(Continued)

TABLE 5. *Continued*

Study	Compound	Mechanism of Action	Trial Design (AAN Class of Evidence)	Diagnosis	Patients (n)	Follow-up Period	Outcome Measure(s)	Results
David et al., 2015	Modfied Fitness Counts (mFC) vs. Progressive Resistance Exercise (PRE) programs	Exercise	Randomized, controlled trial (Class IV—per article)	PD patients, MMSE ≥23	Screened for eligibility: 70 Followed: 51 Study completers: 38	24 months	Step Test, Single/ Dual Timed Up and Go, dual-cognitive task, dual-manual tasks); PDQ-39, FOG, SF-12 Secondary: AEs, attrition Primary: UPDRS part 3 (*off*) score Secondary: Digit Span, Stroop, BTA	gains maintained 10 to 12 weeks after intervention Significant improvement in Digit Span and Stroop in mFC group and Digit Span, Stroop, and BTA in PRE group

BTA, Brief Test of Attention; BVMT, Brief Visual Memory Test; CES-D, Center for Epidemiological Studies Depression Scale; COWAT, Controlled Oral Word Association Test; FOG, freezing of gait; GDS, Geriatric Depression Scale; HVLT, Hopkins Verbal Learning Test; JLO, Judgment of Line Orientation; PASAT, Paced Auditory Serial Addition Test; PD-Q, PD Questionnaire; ROCFT, Rey-Osterrieth Complex Figure; SF, Short Form; SRT, Selective Reminding test; TOM, Theory of Mind; WHO-DAS, World Health Organization Disability Assessment Schedule.

44 PD patients assigned to either the cognitive training group (REHACOP, specific modules on different cognitive domains and tasks, allocated over a set time period) or a control group (occupational activities by a psychologist, e.g., drawing, reading, paper or wood constructive tasks) with 3 sessions per week for 3 months.[58] Primary outcomes were changes on multiple cognitive measures (i.e., processing speed, visual memory, executive function, and theory of mind), with secondary outcomes focusing on neuropsychiatric symptoms and functional disability. Almost all subjects completed the post-test assessment (95%), and there was a significant improvement in processing speed, visual memory, theory of mind, and functional disability in the active group. A recent study tested a computer-based training program for attention and explored its effect on brain activity using fMRI, though over 100 subjects had to be screened to enroll 20, of whom 15 completed.[59] PD subjects were randomized to a computer-based attention-training program (RehaCom, meeting twice-weekly for 1-hour sessions over 6 weeks) versus control intervention (computerized simple visuomotor coordination tapping task, with 12 sessions, 1 hour each over 6 weeks) and underwent resting-state fMRI pre- and post-intervention. The computer-trained attentional group had significantly improved performance on the Symbol Digit Modality Test (SDMT) and Digit Span Forward, compared to the control group. Resting-state fMRI analyses revealed significant group-by-time interactions on left-sided attention and central executive neural networks (increased activity in the superior parietal cortex and dorsolateral prefrontal cortex, respectively).

Other behavioral intervention trials are ongoing. A randomized, open-label trial of cognitive training in PD-MCI subjects will compare Brain Fitness, InSight program, and an active control (quizzes on computerized program regarding knowledge about literature, art, and history) over 3 months (NCT02225314). Study outcome measures, including percent accuracy on cognitive training quizzes, along with secondary outcome measures of 39-item Parkinson's Disease Questionnaire (PDQ-39) and California Verbal Learning Test (CVLT)-II long delay free recall scaled score. A randomized, double-blind trial will compare the effect of psychosocial cognitive behavioral based training versus nonspecific group training on quality of life and management of daily living in PD-MCI (NCT02048605).

Physical Exercise/Activities

Physical activity and exercise have reported benefits for motor symptoms in PD,[53,60-62] and studies investigating their effects on cognition are growing. Effects of combined physical activity and cognitive training therapies may be potentially additive.[63] To date, the types of physical interventions and exercises examined in PD

cognition have been diverse, including passive cycling, aerobic group exercise, combined aerobic and resistance exercises, and dance, though few controlled studies have been conducted.[64-66] Tabak and colleagues recently described 2 PD patients (1 with PDD, 1 with PD-MCI) who completed an 8-week program of 24 sessions of hour-long stationary bicycle and improved in executive function tasks and MoCA scores; however, these case report findings should be interpreted cautiously given the study design.[67] Another study assessed the effects of tango (20 sessions, 90 minutes each) compared to education lessons over 12 weeks on spatial cognition and disease severity in nondemented PD patients.[68] Compared with the 9 subjects assigned to education lessons, the 24 tango participants had significant improvement in spatial cognition (measured by Brooks Spatial Task) and executive function (measured by MoCA score) as well as balance and disease severity after the 20 sessions, with continued effect at 10 to 12 weeks postintervention. A recent study, following up on previous exercise interventions for motor function in nondemented PD, compared the effect of two exercise regimens (i.e., modified Fitness Counts [18 subjects] and Progressive Resistance Exercise program [20 subjects]) on cognitive outcomes of attention and working memory.[69] At 24 months, there was statistically significant improvement in cognitive measures with the exercise programs, such that the modified Fitness Counts improved Digit Span and Stroop scores, whereas the Progressive Resistance Exercise program also improved Digit Span, but also the Brief Test of Attention. This study suggests that long-term studies of exercise, motor function, and cognition in PD are also feasible.

An ongoing randomized, single-blind study will compare different types of exercise (skill-based exercise, aerobic exercise, or social contact) and examine their effect on cognitive and motor scores, appreciation of exercise, quality of life, and fMRI in a large cohort of PD subjects (NCT02267785). Another ongoing study will examine the effects of treadmill exercise, computerized cognitive training, or their combination on executive function, dual task abilities, and instrumental ADLs at 3 months in 121 PD subjects (NCT01156714).

Neuromodulation

Noninvasive brain stimulation techniques, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation have been applied to treat various neuropsychiatric conditions (e.g., mood disorders, migraines, stroke, and AD). Though several preliminary studies have examined these techniques in PD cognitive impairment, to date, there is insufficient evidence to support its use for cognitive enhancement and additional studies are completed or underway.[54,55,70-75] Previous controlled studies in PD include several rTMS trials with sham conditions, though several have also included depressed patients and depression outcome measures. Results suggest that positive effects of rTMS on executive function tests may occur independently of mood effects and that gains may occur in some cognitive tests (executive function, Stroop, Tower of London), but not others (MMSE, Trail Making Test [TMT], and Frontal Assessment Battery [FAB]).[72-75] From the ClinicalTrials.gov website, there is an ongoing trial using "real" TMS compared to sham TMS in a randomized, double-blind trial of PD cognitive dysfunction. The primary outcome measure is the change in magnetoencephalography (MEG) connectivity after 2 weeks of intervention and, secondarily, changes in cognitive tests for global cognition, attention, executive function, memory, language, and visuospatial function (NCT02346708).

Clinical Implications

Clinical trials in PD cognitive impairment are critically important given that cognitive deficits, particularly at the stage of dementia, are associated with poor outcomes, reduced quality of life, and increased caregiver burden.[2,3] Effective and safe symptomatic therapies for PD cognitive dysfunction, across its full spectrum of clinical deficits, would be welcomed by patients, caregivers, and health care providers. Disease-modifying agents to slow down or halt PD cognitive decline would represent significant therapeutic advances, though none of the trials previously discussed fulfill this. Though the recognition of PD cognitive deficits has increased over recent years, there remains a paucity of investigational agents, and in contrast to ongoing or planned studies in AD, few in PD cognitive impairment utilize novel compounds or incorporate biomarkers. One recent exception is the SYNAPSE trial with a 5-HT6/5-HT2A antagonist, which represents a step toward novel therapeutics, PD-relevant outcome measures, and computerized assessments, thereby moving beyond cholinesterase inhibitors and AD outcomes. An increasing number of symptomatic trials have been conducted in nondemented, but cognitively impaired, PD, including PD-MCI. This emergence coincides with recognition of PD-MCI as a distinct entity with diagnostic criteria and a potential prodrome to dementia.

The clinical trials previously discussed have advanced our knowledge of symptomatic treatments for PDD, DLB, and PD-MCI and highlight unmet needs (see also Future Directions section). The selected trials have expanded our horizon of potential therapeutic interventions with nonpharmacological interventions (e.g., cognitive training, physical activities, exercise, and noninvasive stimulation) and even

neurosurgical techniques. Future studies with rigorous, randomized, controlled trials will be needed to fully assess the clinical implications of these interventions. Several studies now include neuroimaging measures to elucidate the neurobiological effects of therapeutic interventions. As our understanding of biomarkers associated with PD cognitive impairment increases, clinical trials may incorporate these elements into subject selection or outcome measures. Regarding inclusion criteria, most PDD studies have utilized DSM-IV definitions and MMSE ranges or cut-off scores, and future studies will need to incorporate the MDS PDD criteria, analyze effects of interventions on global cognitive abilities as well as different cognitive domains, and assess the impact of treatment on functional abilities, quality of life, and caregiver burden. Similarly, the MDS PD-MCI diagnostic criteria are beginning to be used in clinical trials, though further study of their application and validation is needed. Concerning study designs, PD cognitive clinical trials utilize a variety of primary and secondary outcome measures, and, in some cases, a coprimary outcome, whereas in others, a plethora of secondary measures spanning cognitive, neuropsychiatric, motor, quality of life, and caregiver burden scales. To date, there is no consensus regarding the optimal primary outcome measure or cognitive test(s). The PD cognitive clinical trials range from short-term (10–12 weeks) to longer duration (24 weeks) studies, with some open-label extension phases. Thus, there is a need to understand not only acute, or short-term responses, but also the long-term effects, maintenance of benefit, effect on survival, or delayed onset of AEs. Many studies also demonstrate substantial rates of attrition. Lastly, negative PD cognitive studies underscore the need to determine whether failures are related to small sample sizes, inadequate doses, inappropriate target populations, or sensitivity of outcome measures.

Future Developments

Future clinical therapeutic research in PDD, DLB, and PD-MCI will have to address several issues regarding: (1) therapeutic goals and target outcomes; (2) different types of therapeutic interventions; (3) heterogeneity of PD cognitive impairment; (4) biomarkers or surrogate markers for disease progression and treatment response; (5) comorbid nonmotor and motor features of PD; (6) regulatory aspects; and (7) study design and outcome measures. There is a need for therapeutics that not only improve symptomatic control of PD cognitive deficits, functional independence, and well-being of patients across the cognitive spectrum, but also that provide disease-modification by preventing, halting, or slowing cognitive decline. To date, clinical research trials in PD cognitive impairment have primarily focused on symptomatic effects, but with earlier detection of cognitive deficits, emergence of biomarkers associated with cognitive progression, and development of interventions addressing specific underlying neurodegenerative and neuropathological processes, future trials may be able to test disease-modifying agents. In recent years, symptomatic therapeutic interventions for PD cognition have not been limited to pharmacological strategies, but also have included nonpharmacological interventions (e.g., cognitive training, physical exercise, and neuromodulation). Future nonpharmacological intervention trials will need to address study design issues regarding blinding, optimal control groups, motor demands of tasks, combined effects of mental and physical exercise, long-term outcomes and adherence to these types of interventions, and how they affect the pathophysiology and neural substrates of PD cognitive deficits.

The clinical and neuropathological heterogeneity of PD cognitive impairment is well recognized.[25,76,77] In addition, genetic polymorphisms or mutations (e.g., APOE4, MAPT, or GBA) may influence the presence and degree of PD cognitive impairment.[78-82] Thus, patients with PD cognitive impairment who are enrolled in clinical trials may represent a heterogeneous group, and this heterogeneity may impact clinical trial outcomes. Future studies that stratify or enroll PD patients by cognitive phenotype (e.g., nonamnestic vs. amnestic), genotype, or biomarker profile (e.g., AD-positive vs. AD-negative profile) may help answer some of these questions and identify therapies for distinct PD groups. Biomarkers for diagnosis and progression, including blood, cerebrospinal fluid, and neuroimaging modalities, represent active areas of research in PD cognitive impairment and, ultimately, may provide surrogate outcome measures of symptomatic or disease-modifying efficacy in PD cognitive impairment or for the development of agents targeting synuclein, amyloid, tau, or other proteins. In the field of AD, biomarkers already have been incorporated into diagnostic criteria for MCI and AD and play a role in guiding selection of target populations based on genetic mutations (e.g., dominantly inherited AD mutations or APOE e4 alleles) or neuroimaging presence of amyloid deposition.[83,84]

Clinical trials for PD cognitive impairment also need to consider comorbid nonmotor and motor features of PD. Depression, apathy, sleep disturbances, and psychosis frequently accompany PD cognitive impairment and, moreover, may share neurobiological substrates with PD-MCI and PDD.[7,85-88] These nonmotor features may affect cognitive test performance, and one should cautiously interpret test results in the setting of marked depression, apathy, anxiety, or sleepiness. Gait impairment, falls, and postural instability are associated with worsened cognition and attention.[89-91]

Motor features, such as tremor or bradykinesia, may affect performance on cognitive tests that require manual tasks or are timed, whether pen-paper or computerized.

Other study design issues to consider include cognitive and functional outcome measures. PDD trials, such as the large, randomized, controlled trials with rivastigmine (2004) and donepezil (2012), as well as several for PD-MCI, utilize scales derived from AD, which do not necessarily reflect PD cognitive deficits.[4,20,42] To date, there is no consensus regarding which cognitive test(s) or batteries to use for PDD or PD-MCI trials, whether global or specific cognitive domains should be assessed, which tests are most sensitive to change over time or predict cognitive decline, and which tests can best capture responses to pharmacological or nonpharmacological interventions.[9,92] For drug approval, regulatory agencies may require evidence of functional benefit in trials of MCI. At present, however, there is no clear definition regarding how to best measure the functional impact of cognitive impairment in PD, though several scales have been proposed.[92-95] Future research directions should advance our understanding of the trajectory of cognitive decline; refine or develop test batteries specific for PD cognitive impairment, functional independence, and its associated nonmotor and motor comorbidities; validate biomarkers of PD cognitive impairment and progression; and optimize clinical trial design, patient selection, and outcome measures. ■

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