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FOREWORD

CME

At a Crossroads: Revisiting Mild Cognitive Impairment in Parkinson's Disease

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The relatively recent recognition of the high prevalence and impact (ie, association with excess disability, worse quality of life, poorer outcomes, and increased caregiver burden) of cognitive impairment in Parkinson's disease (PD) has changed how we conceptualize the disease.[1-3] Once thought to primarily affect executive abilities in a minority of patients or to occur only in advanced disease stages, it is now known that a range of cognitive deficits occur and that PD with dementia (PDD) occurs in up to 80% of patients long term.[4,5] A wide range (15%-40%) of PD patients meet study-specific criteria for mild cognitive impairment (PD-MCI),[6] and cognitive deficits have been reported in newly diagnosed[7,8] and even prodromal PD.[9] These latter findings have contributed to recently proposed revised clinical diagnostic criteria for PD,[10] which allows for dementia to be a comorbid condition at the time of PD diagnosis. Diffuse cortical Lewy body disease pathology is the major contributing pathology to PDD,[11] but a substantial percentage of PDD patients, and an even higher percentage of dementia with Lewy body (DLB) patients, also meet criteria for comorbid Alzheimer's disease.[12,13] Various PD dopaminergic pharmacotherapies appear to have little long-term impact on cognitive outcomes[14] but can adversely impact cognitive abilities in impaired patients, whereas deep brain stimulation surgery is associated with cognitive decline,[15] although there are likely differential effects based on baseline cognitive status, age, disease severity, comorbid psychiatric conditions, and possibly lead trajectory and placement. A range of neurotransmitter deficits (eg, acetylcholine, dopamine, and norepinephrine) and genetic mutations (eg, Apolipoprotein E4(*APOE* e4), Brain-derived neurotrophic factor (*BDNF*) val66met, Catechol-O-methyltransferase (*COMT*) val158met, microtubule-associated protein tau (*MAPT*), and glucocerebrosidase (*GBA*) polymorphisms) have been implicated in PD cognitive impairment. There have been significant advances in the assessment of PD cognitive impairment (eg, screening instruments, rating scales, and consensus diagnostic criteria for both PDD[16] and PD-MCI[17] that provide a framework and support consistency across research efforts, but these diagnostic advances have yet to translate into significant treatment advances, with only 1 large positive therapeutic study for PDD,[18] and no positive large-scale studies for PD-MCI.[19]

The lack of symptomatic and disease-modifying interventions for cognitive impairment in PD is partially attributable to its complex underlying pathology, the heterogeneous nature of PD phenotypes, and the variable inclusion of validated assessment and clinical outcome measures sensitive to detect short- and long-term cognitive change. In 2013, a Regulatory Roundtable for Cognitive Impairment in PD was held with the aim to incentivize field-wide consensus of PD-MCI criteria and therapeutic development paths.[19] Recommendations from this roundtable took into consideration the Food and Drug Administration (FDA) guidance on having co-primary indicators of significant cognitive improvement plus functional benefit in therapeutic cognitive clinical trials in PD. Since the 2013 roundtable, studies have been completed or are ongoing to evaluate the prognostic and diagnostic utility of existing and newly developed cognitive, functional, and outcome measures,[20-22] including MDS-proposed level 1 versus level II PD-MCI diagnostic

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criteria, that will enable a distinct regulatory path for therapeutic development for PD-MCI treatments. However, a single co-indicator of clinically relevant change in cognition and function does not exist for PD cognition. It is against this background that the Michael J. Fox Foundation for Parkinson's Research convened its Cognition Advisory Committee and invited experts in May 2017 to appraise the current PD-MCI landscape and determine whether the field has made sufficient progress in recent years to justify clear recommendations to the Food and Drug Administration on trial design and outcome measures for clinical trials focused on PD-MCI.

The four additional articles in this miniseries focus on the following key aspects of PD-MCI: (1) definitions and diagnostic criteria, (2) neuropsychological assessment and epidemiology, (3) biomarkers, and (4) recent, current, and future clinical trials. The articles summarize mostly recent research and progress in these rapidly evolving areas, illustrate challenges, and highlight opportunities moving forward. Some key, unsettled, or controversial issues are also discussed, including the ongoing use of many different cognitive screening instruments and neuropsychological tests across studies; determining the optimal subtyping of cognitive impairment; lacking consensus on optimal outcome(s) in cognition clinical trials (a controversial issue in the Alzheimer's disease community as well); determining if cognitive decline has occurred compared with one's premorbid state; assessing functional abilities related to cognition; choosing inclusion/exclusion criteria for cognition-focused clinical trials; accounting for numerous, common, comorbid nonmotor symptoms (eg, psychosis and depression); including biomarkers either as part of inclusion/exclusion criteria or as an outcome measure; dealing with the high prevalence of comorbid Alzheimer's disease pathology in PD patients with significant cognitive impairment; ongoing controversy regarding the relationship between PDD and dementia with Lewy bodies; developing research infrastructure worldwide to support the conduct of clinical trials in PD patients focused on cognition; and identifying novel symptomatic and disease-modifying compounds to be tested.

Significant cognitive impairment is a common and much-feared outcome in PD. Patients and loved ones suffer tremendously as a result, and clinicians have limited therapeutic options to date. PD cognitive impairment remains a large and unmet challenge to the research, funding, and patient communities. We hope that this miniseries sheds light on this important topic and helps point the way forward to ameliorating the cognitive deficits and decline in PD. ■

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