Alzheimer's & Dementia 12 (2016) 75-84

Review Article

Development of a patient-reported outcome instrument to assess complex activities of daily living and interpersonal functioning in persons with mild cognitive impairment: The qualitative research phase

Mark Forrest Gordon[a,*], William R. Lenderking[b], Amy Duhig[c], Julie Chandler[d], J. Jason Lundy[e], David S. Miller[f], Elisabeth Piault-Louis[g], Rachelle S. Doody[h], Douglas Galasko[i], Serge Gauthier[j], Lori Frank[k], on behalf of the Patient-Reported Outcome Consortium's Cognition Working Group

[a]*Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA*
[b]*Evidera, formerly United BioSource Corporation (UBC), Lexington, MA, USA*
[c]*Xcenda, Palm Harbor, FL, USA*
[d]*Merck, Kenilworth, NJ, USA*
[e]*Outcometrix, Tucson, AZ, USA*
[f]*Bracket, Wayne, PA, USA*
[g]*Genentech, South San Francisco, CA, USA*
[h]*Alzheimer's Disease and Memory Disorders Center, Baylor College of Medicine, Houston, TX, USA*
[i]*University of California, San Diego, School of Medicine, San Diego, CA, USA*
[j]*McGill Centre for Studies in Aging, Montreal, Canada*
[k]*Patient-Centered Outcomes Research Institute (PCORI), Washington, D.C, USA*

Abstract

Introduction: As drug development research efforts move toward studying patients earlier in the course of Alzheimer's disease (AD), it is important to incorporate the patient's perspective into measurement of outcomes.
Methods: This article summarizes the qualitative work of the Patient-Reported Outcome Consortium's Cognition Working Group in the development of a new self-reported outcome measure in persons with mild cognitive impairment (MCI) due to suspected AD, herein referred to as MCI.
Results: The draft measure captures the patient's voice for two functional domains, complex activities of daily living and interpersonal functioning.
Discussion: This work represents a series of initial steps in the development of this rating scale. The next steps are to conduct psychometric analysis and evaluate the role of insight.

Keywords: Cognition; Mild cognitive impairment; Alzheimer's disease; Patient-reported outcome; Activities of daily living; Interpersonal functioning; Qualitative; Critical Path Institute

1. Introduction

Prodromal Alzheimer's disease (AD) [1] and mild cognitive impairment (MCI) due to suspected AD [2], herein referred to as MCI, have recently emerged as important targets for new treatments (Table 1). In 2013, the Food and Drug Administration (FDA) published its draft guidance [3] regarding drug development efforts for "early AD," including "predementia." Given the advances that make

Conflict of interest: A.D. was an employee of AbbVie during the time the article was written. D.S.M. is a full-time employee of Bracket. Bracket was part of UBC at the time the research was conducted; however, Bracket was independent of UBC during the preparation of this article. W.R.L. is a full-time employee of Evidera, formerly UBC. R.S.D., D.G., and S.G. received honoraria for their participation as members of the expert panel. The other authors do not report any conflicts of interest regarding this article.

*Corresponding author. Tel.: +1-203-791-6871; Fax: +1-203-798-4037.
E-mail address: mark.gordon@boehringer-ingelheim.com

http://dx.doi.org/10.1016/j.jalz.2015.04.008
1552-5260/

Table 1
Core clinical criteria for diagnosis

Mild cognitive impairment due to Alzheimer's disease and prodromal AD [2]
For use by health care providers without access to advanced imaging techniques or cerebrospinal fluid analysis:
1) A concern about a change in cognition, whether that concern comes from the patient, a significant other, or a clinician
2) evidence of impairment in one or more cognitive domains (most commonly episodic memory)
3) independence in functioning (note that considerable impairments may be present before independence is lost)
4) the patient is not demented
Prodromal AD/amnestic syndrome of the hippocampal type [1]
1) A very poor free recall
2) A decreased total recall due to an insufficient effect of cueing

Abbreviation: AD, Alzheimer's disease.

prevention of disease progression from MCI to AD possible, quantifying disease state and measuring change over time in very early disease are critically important goals. Existing measures used to quantify treatment effects in mild-to-moderate AD may not be sufficiently sensitive to capture the more subtle cognitive and functional impairments that persons with MCI experience. Some functional impairment may begin during the predementia (MCI) phase of AD [4,5].

The concept of function covers a large territory, including basic activities of daily living (ADLs), instrumental ADLs (IADLs), complex ADLs (cADLs), and interpersonal or social functioning, among others. Impairments in higher order cADLs, such as financial capacity, social planning, complex verbal facility, and other skills and activities related to executive function, may be among the earliest deficits in persons with MCI [4,6,7]. Furthermore, people with MCI may note deficits in some activities, such as reading, long before the deficit is observable to others [6,7]. This supports the value of including patient-reported outcomes (PROs) in this population. Reading speed and comprehension are also activities in which deficits are likely to be noticed by the person early on but unlikely to be detected by others except through specific neuropsychological testing. Higher order functioning opens an area to explore for outcome measurement development and people with MCI may be the best source for describing the earliest deficits.

Further support for the need for a PRO measure for persons with MCI comes from the clinical trials literature. Doody et al. [6] suggested that patients may be the first to notice changes in their symptoms, even when other instruments are not sensitive to such changes. In this 48-week randomized placebo-controlled clinical trial of donepezil, scores at weeks 24 ($P = .05$) and 48 ($P = .02$) on the Perceived Deficits Questionnaire favored patients on active treatment relative to those on placebo. This positive effect was consistent with that seen on the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) at end point and the patient and caregiver global assessments at some time points during the study.

To date, most instruments developed to assess cognition and function in patients with MCI have relied on informant report, either partially or fully, such as the measurement of everyday cognition (eCog) [8] (PRO version in development, personal communication from ST Farias to WR Lenderking, May 2, 2014). Only a few instruments have relied on the patient report alone. Recognition of the value of PRO assessment in patients with MCI has led to the development of a limited number of self-report instruments. For example, the Alzheimer's Disease Cooperative Study (ADCS) has developed instruments for use in prevention studies [9] to assess domains judged by clinical experts to be important in MCI and AD. Self-reported questionnaires that assess cognitive function and ADLs have been administered in studies of patients with early disease. Examples include the Alzheimer's Disease Cooperative Study-Activities of Daily Living-Prevention Instrument (ADCS-ADL-PI) [9] and the cognitive change checklist [10,11]. Although studies, such as Galasko et al. [9], have demonstrated the feasibility and reliability of self-report in the target population, the self-report tools were largely adapted from existing instruments and developed by clinical experts without input from patients. The existing self-report tools may therefore not adequately detect an early change in the target MCI population.

Frank et al. [12] developed the Patient-Reported Outcomes in Cognitive Impairment (PROCOG), a patient-reported instrument that assesses symptoms and impact of MCI. Item development was based on existing literature on MCI and AD symptoms, input from experts, and concepts elicited from focus groups with patients and caregivers. Acceptable psychometric properties, including test-retest reliability and internal consistency, demonstrated the feasibility of self-report in the MCI target population [12]. Although domains include some aspects of functioning, the PROCOG was not developed to comprehensively capture key aspects of functioning in MCI. There remains a need for a measure developed using best practice, including obtaining appropriate input from persons with MCI and caregivers, that addresses the functioning domains most relevant to the early disease experience.

The aim of the Cognition Working Group (WG) of the Critical Path Institute's PRO Consortium was to develop a new PRO instrument to be qualified by the FDA as a "fit for purpose" efficacy end point in clinical trials of patients with MCI. Instrument development is being guided by the FDA guidance documents titled PRO Measures: Use in