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Reliability of a cognitive endpoint for use in a multiple sclerosis pharmaceutical trial

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ABSTRACT

Objective: Determine reliability and basic psychometric properties of a composite cognitive endpoint, MS-COG, for monitoring change in cognitive function in MS drug trials.
Background: 50% of MS patients have cognitive impairment that impacts ability to work and quality of life. We selected neuropsychological tests based on sensitivity to MS cognitive impairment, availability of alternate forms, cross-cultural utility, and feasibility for multicenter trials, and assessed the reliability and validity of a composite endpoint, MS-COG.
Design/methods: Administered SRT, BVMT-R, PASAT, and SDMT to 60 MS patients at 4 US centers twice over 45 days, along with symptom inventories by patients and informants.
Results: The MS-COG had test–retest reliability of 0.91. Processing Speed and Memory indices had reliabilities of 0.89 and 0.86, with modest practice effects. Reliability was high for the RR MS and SP MS subgroups as well, with correlations of .90 and .93, respectively for MS-COG. Overall, 42% of subjects obtained MS-COG scores in the impaired range, with SP MS subjects performing 0.8 SD below RR MS subjects. Impairment correlated well ($r = 0.37$ to 0.40) with informant reports but was inconsistent with patient report, with the least reliable assessments by those with greater symptom severity.
Conclusions: The MS-COG is a reliable, repeatable measure of MS cognitive functioning that is sensitive to cognitive impairment in SP MS and RR MS patients and feasible for multicenter clinical trials. Further development is warranted.

1. Introduction

Cognitive Impairment Associated with Multiple Sclerosis (CIAMS) [1] is common, with frequencies ranging from 40 to 75% reported in clinical samples [2–5] and meta-analyses [6–10], with estimates varying according to the definition of cognitive impairment. Processing Speed and Learning/Memory are the domains identified as most likely to be impaired in individual MS subjects with frequency rates estimated at approximately 52% and 54%, respectively, [11,12] with impairment in each domain manifesting at differing levels of severity within individual patients [13]. These cognitive impairments are relatively independent of MS symptoms that cause motor impairment [6,14] and comprise a significant contributing factor to overall disability and lessened quality of life [15]. A pharmaceutical therapy that improves cognitive functioning in MS patients would therefore be of considerable value in the overall management of MS. However, in order to assess the effectiveness of pharmaceutical interventions, reliable and valid indices of meaningful cognitive change that are feasible for multicenter clinical trials are required.

The present study sought to determine the reliability of a composite endpoint (MS-COG) for use in determining efficacy of disease modifying pharmaceutical agents in the improvement of cognitive functioning in MS patients. An *a priori* composite endpoint merits investigation as similar composite endpoints for other disease entities that have been required by FDA in past trials [16–18]. In addition, a composite endpoint

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offers a number of potential general advantages, such as lower error rates, improved reliability, and greater simplicity in summarizing treatment effects and relating clinical meaningfulness of the observed changes [16–19]. There are, of course, disadvantages in collapsing multiple domains into a single endpoint, including potentially decreased sensitivity in comparison to a single endpoint and greater difficulty in interpretation of any change identified. In regard to the former, when a pharmaceutical agent aims to improve cognitive functioning generally, focus on change in an individual domain may potentially disproportionally represent improvement in a given subject if such gains are not present in other domains. We therefore recommended combining multiple domains in a single endpoint. In regard to the latter, clinical interpretation of the composite endpoints will still require scrutiny of the underlying factors.

Although there have been a number of MS studies examining potential improvement due to the effects of a pharmaceutical agent on individual tests of cognitive functioning over the course of a trial [20–22], little research has been published examining the effects of such an agent on general neuropsychological test performance in MS. An earlier investigation by Fischer et al. [23] examined the effects of intramuscular interferon beta-1a (Avonex®) in MS patients using a comprehensive neuropsychological test battery administered over a 2 year time span in a subset of English speaking subjects from the Phase 3 registrational clinical trial (MSCRG study). Tests measuring Learning, Memory, and Processing Speed were group together *post hoc* as being the most frequently impaired domains. A significant improvement of approximately 0.5 standard deviations was identified for Avonex over placebo. Subsequent efforts by Rao [24] and Benedict et al. [25] demonstrated that briefer assessments than used by Fischer et al. might be useful for identifying cognitive impairment in MS, but their operational feasibility has limited their use in drug trials.

The current project began when Biogen Idec recruited a panel of advisors with extensive experience in research on cognitive impairment in MS clinical pharmaceutical research populations (authors DE, RB, FF, JW, and JD). In recommending tests for the current research, the advisory panel considered not only the sensitivity of the proposed component tests to MS impairment, but also test–retest reliability, the availability of multiple alternate forms for longitudinal studies, suitability for administration by newly trained clinical staff, and the feasibility for use in cross-cultural and linguistic settings. In considering these factors, the expert panel chose the Paced Auditory Serial Addition Test (PASAT) [24,26], Selective Reminding Test (SRT) [27], Symbol Digit Modalities Test (SDMT) [24,28], and Brief Visuospatial Memory Test — Revised (BVMT-R) [29] to cover the two cognitive domains most affected in MS, information processing (PASAT and SDMT) and Learning and Memory (SRT and BVMT-R). Notably, these tests were identified by Strober et al. [30] as having optimal sensitivity to detect impairment in the MS population, with effect sizes ranging from $d = 0.7$ to $d = 1.1$, which was not the case for tests of other domains included in previous MS Cognitive Batteries such as executive functions, language, and visuospatial judgment [31].

The current study sought to establish the basis for combining the neuropsychological measures selected by the expert panel into a single endpoint, the MS-COG, for use in pharmaceutical research, and determine basic psychometric properties related to reliability. An investigation of the relationship of the endpoint to the observations of the patient and their designated caregiver on real world cognitive function was also investigated.

2. Methods

2.1. Participants

Subjects were recruited from existing patient lists from four MS centers in the United States, each recruiting 15 patients with documented history of Relapsing–Remitting (RR) or Secondary Progressive (SP) MS. Participants who agreed to enroll were paid $60. Participants were included regardless of MS severity, presence of cognitive impairment, or duration of illness so as to be representative of MS clinic patients generally. Exclusion criteria included physical or sensory impairment that might preclude completion of cognitive test protocols, untreated major depressive and/or untreated anxiety disorder of sufficient severity to potentially to impact cognitive skills, history of severe psychiatric illness such as bipolar disorder or schizophrenia, or severe traumatic brain injury or other medical illnesses that would preclude valid completion of the assessments. One subject was excluded after enrolment because of the onset of clinically significant symptoms of depression following Study Day 1 and which were of sufficient severity such that the subject was unable to travel to the research site. All other patients were neurologically and psychiatrically stable for the duration of the study.

Demographic characteristics of the sample identified the group as typical of clinical MS populations [12] as well as of populations recruited for pharmaceutical studies [22]. The group was comprised of 43 women (72%) and 16 men (28%) recruited from lists of patients diagnosed with MS according to McDonald criteria in 4 U.S. clinics, with an average age of 47.9 (SD = 7.9; range = 26–61). A majority (77%) were receiving disease modifying therapy. Average time since diagnosis was 13.2 years (SD = 8.5; range = 1–33). Similar to reported studies of other clinical MS populations, the majority (87%) were Caucasian, with 5% identifying as African-American, 5% as Hispanic, and 3% as other; only 2% were not high school graduates, with 27% having a high school degree or GED, 18% an Associate Degree, 28% a Bachelors Degree, 21% a Masters Degree and 5% an advanced degree; the median Expanded Disability Status Scale (EDSS) [32] was 2.5 and the mode was 2; approximately 77% of participants had a diagnosis of RR MS and 23% one of SP MS; [12,24,33]. As might be expected, the group diagnosed with SP MS was significantly older than that of patients with RR MS (55.1 ± 5.6 years *vs.* 47.9 ± 9.2 years) and had significantly higher EDSS ratings (4.2 ± 1.8 *vs.* 2.2 ± 1.5). The groups did not differ in regard to education or ethnicity.

2.2. Procedures

Participants were assessed at two time points, approximately 45 days apart. Each participant completed the SDMT Oral Version, PASAT, BVMT-R, and SRT on each occasion. A 45 day retest interval was chosen based on clinical observations that this was sufficient for identification of change on measures of memory in a prior MS study [22,34]. Order of test administration was as follows: SRT and BVMT-R Learning Trials, SDMT, PASAT 3- and 2-second trials, SRT Delayed Recall, BVMT-R Delayed Recall. Total time for administration was approximately 30 min. Equivalent alternate forms were used to minimize form-specific practice effects. Self-report forms—the Multiple Sclerosis Quality of Life-54 (MSQOL-54: cite), the Memory Functioning Questionnaire (MFQ) [35] and the Multiple Sclerosis Neuropsychological Questionnaire-Patient (MSNQ-P) [36,37] were administered prior to the neuropsychological tests in order to limit the degree to which a subject based her/his opinion on test performances. The Multiple Sclerosis Neuropsychological Questionnaire-Informant (MSNQ-I) [36,37] as completed at the convenience of the caregiver without knowledge of actual test performance and returned to the investigator.

2.3. MS-COG test instruments

2.3.1. Symbol Digit Modalities Test (SDMT)

In this measure of Processing Speed and Working Visual Memory, the subject is given 90 s to pair specific numbers with given geometric figures based on a reference key using an oral response, to limit problems due to dexterity in MS patients [24]. At Study Day 1 the original, WPS-published form was administered [28] and at Visit 2 Rao's Form 2 [38] was administered.

2.3.2. Paced Auditory Serial Addition Test (PASAT)

First developed by Gronwall to assess patients recovering from concussion [39], the PASAT requires patients to monitor a series of 61