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Background and literature review of patient-centered treatments for gait impairments in individuals with multiple sclerosis

The current definition of a treatment "responder" (to pharmacological management) for gait impairments in individuals with multiple sclerosis (MS) is controversial for lacking patient-centeredness and failing to capture meaningful walking change. A common outcome used to determine whether a patient is responding to walking treatments (both pharmacological and rehabilitative) is gait speed. In studies involving the pharmacological "walking drug," dalfampridine extended-release (D-ER, Ampyra®), treatment failure is defined as less than 20% improvement in gait speed.[1,2] However, is faster walking an indicator of improvement from the perspectives of patients, or even clinicians for that matter? The studies that informed the above definition of treatment responder by gait speed have typically defined clinical meaningfulness by employing various objective measures, such as maximal distance subjects walk (Dmax)[3] and changes in walk time (gait speed) during an MS exacerbation.[4] Based on several interviews conducted for this research project, walking "better" does not typically equate with walking faster; rather, many patients and clinicians alike find meaning in improved safety (e.g. less falls), increased independence with walking, increased endurance (i.e. less fatigue and longer walking duration), and increased participation in community ambulation (i.e. increased ease of shopping and working outside the home).

In the pharmacological studies mentioned above, a large majority (60%) of patients on D-ER, Ampyra fail to respond (in terms of gait speed) to drug treatment alone.[1,2] To evaluate the benefit of a physical therapy program involving gait training and exercise as an alternative or adjunct treatment for this patient group (and a broader population of individuals with MS and walking difficulties), meaningful treatment outcomes first need to be identified to elevate patient-centered care. A better understanding of therapists' decision-making processes and the identification of meaningful treatment strategies and patient-centered outcome measures will allow for better informed future research studies and excellent quality clinical practice.

High-quality, value-based care must incorporate the perspectives of both the clinician and the patient into treatment approaches and patient outcomes, yet currently, there are few studies in the literature that define "clinically meaningful improvement" in walking-related outcomes for people with MS. One statistical value that is often used to assign clinically meaningful improvement is the "minimal clinically important difference" (MCID). The MCID is defined as the smallest change of a score in an outcome measure that is perceived by the patient as beneficial. Meaningful change can be interpreted differently, and MCID values are therefore context-specific and provide an estimate for a specific population at a particular stage of recovery. Furthermore, there are various methods in the literature to determine MCID. How do rehabilitative studies that utilize MCIDs for gait measures in individuals with MS compare to the definition of meaningful walking change in pharmocological studies (i.e. >20 increase in gait speed)? Are patient's perspectives and values being incorporated into the methods to define MCIDs in rehabilitative studies?

To address these questions, a literature search was performed in PubMed for "minimal clinically important difference" (OR MCID) AND "multiple sclerosis" (MeSH terms). This search yielded 13 results, 5 of which were relevant to outcome measures used for walking or mobility. Literature results included studies relating to the Berg Balance Scale (BBS), the Multiple Sclerosis

Walking Scale-12 (MSWS-12), the Neurological Fatigue Index for multiple sclerosis (NFI-MS), comfortable gait speed, and steps taken per day. These articles are briefly discussed here to illustrate how MCID values are determined in various rehabilitative studies involving patients with MS and walking impairments.

The BBS has 14 static and dynamic balance activity items to objectively measure static balance and fall risk in adult populations.[5,6] Based on patient performance, each item is scored by the clinician from 0-4 and the items are summed for a maximum of 56, where higher scores indicate better performance. A cohort study by Gervasoni et al. sought to define clinically meaningful patient improvement on the BBS in people with MS (n=110) in response to balance and gait rehabilitation at both inpatient and outpatient settings.[7] To determine the MCID for the BBS, they used an anchor-based approach by comparing BBS scores with clinical global impression of improvement in balance with the Activities-specific Balance Confidence [ABC] Scale, a subjective patient-report outcome (PRO) measure of balance confidence. The MCID was defined as the smallest change in the BBS score from pre- to post-intervention that was needed to perceive at least a 10% improvement on the ABC scale. Using an anchored approach to the ABC, this study determined the MCID for patient-perceived change in balance on the BBS was 3 points for the whole sample of individuals with MS (3 points for the inpatients and 2 points for the outpatients).[7]

The Multiple Sclerosis Walking Scale-12 (MSWS-12) is a subjective measure used to capture the degree that MS impacts an individual's walking ability and functional mobility.[8,9] The 12 items represent walking limitations experienced over the last 2 weeks and include walking, running, standing, climbing stairs. Each item is scored on 1-5 point scale, where 1 indicates no limitation and 5 indicates extreme limitation. Points are summed for a maximum score of 60 to determine a percentage score (0-100%); higher scores indicate a greater disease impact on walking. The MSWS-12 has gained popularity as a PRO in clinical trials due to its strong psychometric properties and established MCID values.[10] MCID values of 4- and 6-point changes were established from recommendations of the IMMPACT group and secondary analyses of data from fampridine-related clinical trials.[10,11] However, no studies had investigated whether the MSWS-12 MCID values corresponded to objective walking measures. A study by Motl et al. examined the validity of MSWS-12 MCID values based on convergent changes (n=82 people with MS and moderate disability) in performance of the Timed 25-ft Walk (T25FW) and 6-min Walk (6MW) tests, temporal-spatial parameters of gait (functional ambulatory profile (FAP) score), and accelerometry (number of steps per day) over a 6 month period in the absence of an intervention.[10] The authors hypothesized that the MSWS-12 MCID values would correspond with changes in objective walking measures; however, no associations were found between groups (stable, worsened change, or improved change) based on either 4- or 6-point MCID values. In fact, such MCID score changes were only associated with change in the Physical subscale score of the Multiple Sclerosis Impact Scale-29 (MSIS-29)[12], another PRO measure to assess disease impact. The results by Motl et al. suggest MCID values for the MSWS-12 may not correspond to standard objective walking measures (e.g. gait speed), but rather they distinctly reflect a patient's perception of physical health status.[10] This interpretation has important clinical implications for clinicians who may use subjective measures such as the MSWS-12 to assess walking improvements. While understanding a patient's perspective about treatment response is important, objective and subjective measures should not necessarily be used interchangeably, as subjective change does not always equate with objective change, and the relationship depends on the particular aspects of walking that are measured.

The Neurological Fatigue Index for multiple sclerosis (NFI-MS) is a PRO used to assess fatigue in patients with MS.[13] The NFI-MS has 12 items, an 8-item Physical scale and a 4-item Cognitive scale as well as a 10-item Summary scale. A study by Mills et al. (n=208 individuals with MS) determined MCID values for the NFI-MS scales and examined the concordance of NFI-MS change scores with the subject's global perception of change.[14] The NFI-MS was implemented before and 6–8 weeks after an intervention/ event likely to affect fatigue levels (e.g. a relapse, pregnancy, or change in drug therapy). At the second time point, participants' global perceived change was assessed with the phrasing, 'Compared to 6 (or 8) weeks ago, my fatigue is,' and the 5 response options ranged from 'much better' to 'much worse.'[14] The NFI-MS MCID was calculated as the largest of the upper or lowest 95% confidence interval for the mean differences (pre- and post-test scores) in the 2 groups rated as either 'worse' or 'better' by the participants. Relatively small MCID values (10% of the scale range or less) were in accordance with subjects' perceived direction of change. Using a published nomogram to convert the subjects' raw scale scores into interval scores, the largest MCID equated to 2.49 points on the Summary scale (30 point range) and 2.36 points on the Physical scale (24 point range).[14] Mills et al. remark on the desirability of their reported small MCID values, as the NFI-MS MCIDs can capture patient-centered, small yet meaningful changes in fatigue.[14]

A systematic review by Bohannon and Glenney evaluated MCID values for comfortable gait speed of adults with various pathology, including MS, in an effort to consolidate information on meaningful changes in walking speed.[15] They reviewed 7 articles that reported MCID values for comfortable gait speed measurements (and excluded articles if the MCID was not calculated using receiver operating characteristic (ROC) curve analysis). The authors emphasized the value of ROC analysis, which identifies an MCID based on a cut point that maximizes sensitivity and specificity, as the most valid and unbiased method to determine MCID values.[15] Of the studies reviewed, only 3 of 7 reported areas under the curve (AUCs) exceeding 0.70, a common criterion value of a 'clinically useful' test (or MCID).[15] Populations by pathology included stroke, hip fracture, mixed, and MS (n=1). Their review identified 13 different anchors (no 2 studies utilized the same anchor) across the 7 studies to determine MCID values for gait speed, the majority of which were between were between 0.10 and 0.20 m s^{-1}, with a median of 0.14 m s^{-1}. Studies reporting AUCs greater than 0.70 ('clinically useful') reported MCIDs of 0.10–0.17 m s^{-1}. The study in their review that involved individuals with MS (n=109), by Paltamaa et al.[16], used the following anchors to determine MCIDs for gait speed (measured over 10 m at baseline and at 1 and 2 yrs): participants' perception of change in health (Short Form 36): 0.14 m s^{-1} (0.69) and the clinicians' perspective of change (Expanded Disability Status Scale): 0.08 m s^{-1} (0.64), where the value in parentheses is the AUC. Hence, a relatively larger increase in gait speed was required to achieve meaningful change from the patient's perspective, compared to the clinician's perspective (EDSS). The authors concluded that changes in gait speed of 0.10 to 0.20 m s^{-1} may be clinically important across different patient groups, despite the various methods used to determine MCIDs across studies.[15]

Lastly, a study by Motl et al. determined MCID values for steps taken per day as an outcome of "free-living walking behavior" in people with MS.[17] They performed a secondary analysis of de-identified data from 15 studies totaling 786 individuals with MS and 157 healthy controls. All participants wore an accelerometer or pedometer over a 7-day period, and patients with MS completed the MSWS-12 and the Patient Determined Disease Steps (PDDS) scale. They analyzed steps/day across 10-point incremental changes of MSWS-12 scores. The PDDS scale, a PRO to assess subjective disability status, was used as an alternative to the EDSS.

Subjects were categorized by their level of assistance for ambulation based on PDSS scores. Steps/day were analyzed across 1-point incremental increases in PDDS scores (consistent with 1-point changes in EDSS). MCID values were determined using regression analyses and analysis of variance (ANOVA) for between group differences. Regression analysis of steps/day on PDDS and MSWS-12 scores was carried out to estimate the incremental change in steps/day per unit change in walking impairment and disability.

Regression analysis by Motl et al. indicated that every 10-point increase in MSWS-12 scores (greater disease impact) yielded a reduction of 642 steps/day and every 1-point increase in PDDS scores (increased disability) yielded a reduction of 915 steps/day.[17] The mean MCID across both self-report scales that captured subtle, patient-perceived changes in walking was 779 steps/day (14% of the mean steps/day for the MS sample). The mean MCID for clinical and health outcomes (e.g. MS type, duration) was 1,455 steps/day (26% of mean score). Finally, the MCID for the cumulative impact of MS (MS vs. control) was 2,747 steps/day (48% of mean score). These MCID values, which range from 14% to 48% of the mean steps/day for the MS sample, reflect the smallest clinically important change in walking behavior in this sample of people with MS to a larger cumulative impact of MS (compared with healthy controls). The authors conclude that a change of 800 steps/day represents an estimated clinically meaningful change in “free-living walking behavior” in interventions for people with MS.[17]

Returning to the questions of how rehabilitative studies determine MCIDs of gait measures in patients with MS and how these compare with definitions used in pharmacological studies, this brief literature review highlights some key differences and implications for current practice and for future studies. The rehabilitative studies described above often used an anchor-based approach to relate MCID values to meaningful change from a patient-perspective (e.g. anchoring to ABC, MSIS-29, and Short-Form 36). Based on this literature review, MS-related rehabilitative research studies are often taking a patient-centered approach when developing MCIDs for gait measures. However, the methods used to calculate MCIDs vary widely, which has the potential to limit systematic analysis and interpretation across studies. Finally, while changes in gait speed, a common objective outcome measure (e.g. Timed 25-Foot Walk), may indicate clinically meaningful change to some patients[18], both pharmacological and rehabilitative studies, as well as clinicians, would benefit from incorporating patient-centered PROs with established MCIDs (e.g. MSWS-12) and objective measures with MCIDs anchored in PROs (e.g. BBS) to aid in the assessment of a patient’s response to a particular walking treatment intervention.

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