Possible clinical outcome measures for clinical trials in patients with multiple sclerosis

Ther Adv Neurol Disord
(2010) 3(4) 229–239
DOI: 10.1177/1756285610374117

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***Abstract*:** Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease with both clinical and pathological heterogeneity. The complexity of the MS population has offered challenges to the measurement of MS disease progression in therapeutic trials. The current standard clinical outcome measures are relapse rate, Expanded Disability Severity Scale (EDSS), and the MS Functional Composite (MSFC). These measures each have strengths and some weakness. Two additional measures, the six-minute walk and accelerometry, show promise in augmenting current measures. MS therapeutics is a quickly advancing field which requires sensitive clinical outcome measures that can detect small changes in disability that reliably reflect long-term changes in sustained disease progression in a complex population. A single clinical outcome measure of sustained disease progression may remain elusive. Rather, an integration of current and new outcome measures may be most appropriate and utilization of different measures depending on the MS population and stage of the disease may be preferred.

***Keyword*:** multiple sclerosis, outcome measures, EDSS, MSFC, six-minute walk, accelerometry

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system with both clinical and pathological heterogeneity [Lucchinetti *et al.* 2000]. Approximately 1 per 1000 persons are afflicted with MS in the United States [Mayr *et al.* 2003; Page *et al.* 1993]. MS is the leading cause of nontraumatic disability in young adults and typically presents during the third or fourth decade in the prime of a patient's personal and professional lives [Frohman, 2003]. The clinical course of MS can vary tremendously between and within patients over time. Patients typically present with either a relapsing or progressive disease course commonly defined by four clinical subtypes: relapsing–remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), primary progressive multiple sclerosis (PPMS), and progressive relapsing multiple sclerosis (PRMS) [Lublin and Reingold, 1996].

Since 1993, five medications have received US Food and Drug Administration (FDA) approval for the treatment of RRMS [Polman *et al.* 2006; Rudick *et al.* 2006; PRISMS Study Group, 1998; Jacobs *et al.* 1996; Johnson *et al.* 1995; The IFNB Multiple Sclerosis Study Group, 1993]. Mitoxantrone (Novantrone) is the only therapy with current FDA approval for SPMS [Hartung *et al.* 1998; Krapf *et al.* 1998]. Therapeutic trials for PPMS and SPMS have remained disappointing overall [Hawker *et al.* 2009; Wolinsky *et al.* 2007; Cohen *et al.* 2002; Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS) Study Group, 2001]. This may be due to failures in our current treatments to alter the progressive disease course, or due to a failure of current outcome measures to detect changes in the progressive stage of the disease or duration of a clinical trial [Ebers *et al.* 2008].

There are several ways to measure disease activity or progression in clinical trials. In general, these could be categorized as objective and subjective measures. Objective measures would include clinical outcome measures and nonclinical outcome measures, such as magnetic resonance imaging (MRI). Subjective measures would cover the gamete of patient-report measures. Patient-report measures can be further classified into measurements of MS-related disease severity or progression [Hobart *et al.* 2001; Sharrack and Hughes, 1999], general health status [Ware *et al.* 1993], MS symptoms [Krupp *et al.* 1989], or quality of life measures [Ritvo *et al.* 1997; Cella

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Table 1. Primary outcome measures for the current FDA approved MS therapies.

Disease-modifying agent	Duration	Primary outcome measure
IFNB -1b (Betaseron) [The IFNB Multiple Sclerosis Study Group, 1993] *versus* placebo	2 years	(1) Difference in annualized relapse rate (2) Proportion remaining relapse free
IFNB-1a (Avonex) [Jacobs *et al.* 1996] *versus* placebo	2 years	Time to onset of sustained worsening in disability (≥1 point change in Expanded Disability Status Scale sustained for 6 months)
IFNB-1a (Rebif) [PRISMS Study Group, 1998] *versus* placebo	2 years	Mean number of relapses during study
Glatiramer acetate [Johnson *et al.* 1995] *versus* placebo	2 years	Mean number of relapses during study
Natalizumab [Polman *et al.* 2006] *versus* placebo	2 years	1 year: rate of clinical relapse 2 year: cumulative probability of sustained disability progression (≥1 point change in EDSS >1.0 at baseline and ≥1.5 point change in EDSS <1 at baseline)

et al. 1996]. In this paper we review current and possible new clinical outcome measures; reviews regarding potential nonclinical outcome measures, specifically MRI and self-report measures, can be found elsewhere [Bar-Zohar *et al.* 2008; Bermel *et al.* 2008; Rudick and Miller, 2008].

Clinical outcome measures

When creating or choosing an outcome measure, the first question is simply, 'What is your outcome of interest?'. The outcome of interest may depend on the available population (e.g. number of subjects) or study duration. This may further depend on the anticipated benefit of the therapy, for example, one may choose to measure relapse rate or postcontrast MRI changes for therapy anticipated to reduce inflammation. Although outcome measure selection may be guided by these external factors, the ideal MS outcome measure would quantify irreversible sustained disease progression. In MS, progression has proven a hard concept to quantify. One must decide which aspects of MS disease progression to capture, e.g., vision, strength, coordination, cognition, fatigue, or daily activity. The pleotropic expression of MS makes it particularly challenging to measure all facets of the disease. Alternatively, one may prioritize the symptoms, for example, the ability to walk may be weighted greater than fatigue.

Measurement of MS disease progression and treatment response is further complicated by: individual patient heterogeneity; population variability in disease course and tempo of progression; subclinical MRI changes of uncertain impact on delayed disability progression; multifaceted neurological deficits with varied abilities for individual patients to compensate; and patient comorbidities. Independently and collectively, these issues have proved challenging for the design of MS therapeutic trials. In addition, cost limitations and practicalities have resulted in studying a chronic disease in snapshot increments, with clinical trials on average occurring over a 2–3-year period in a disease that lasts decades.

Several MS therapies are in phase II and III stages of assessment. The current availability of MS therapies has reduced the opportunity for placebo-controlled trials. Future trials are anticipated to be head-to-head designs, which will require more sensitive outcome measures that are able to detect smaller changes and to detect treatment superiority. The potential for neuroprotective therapies in MS also require optimal clinical outcome measures, which can capture improvement or lack of progression. The standard clinical outcome measures for MS therapeutic trials are relapse rate, Expanded Disability Severity Scale (EDSS), and the MS Functional Composite (MSFC). Relapse rate has been used as the primary outcome measure in most MS therapeutic trials (Table 1) and disease progression has routinely been measured by the EDSS. In the last 10 years, there has been growing interest and application of the MSFC [Fischer *et al.* 1999].

MS relapse rate

Up to 85% of MS patients present with a relapsing–remitting course with an average relapse every 12–18 months in an untreated population. MS relapse is commonly defined as new or worsening symptoms that last 24 hours in duration and occur in the absence of fever or infection [Schumacher *et al.* 1965]. MS relapses have been the primary outcome measure in four of the pivotal MS trials (Table 1). Recognition of an MS relapse in routine practice depends on the patient, who must notify a

clinician about a change in symptoms. Within a clinical trial, relapses can be identified by patient notification or by history and exam changes observed during scheduled study visits.

Traditionally, the number of MS relapses is measured as the event of interest. Additional assessments have included the severity of each relapse, which assumes that the long-term impact of each relapse will depend on the severity. For example, studies have reported the number of 'treated relapses' (relapses that required the use of steroids) as an indication of severity [Durelli *et al.* 2002]. However, there are other factors that might have an impact on the decision to use steroids, and the threshold to administer steroids varies among treating physicians. Currently, there are no formal standards to guide physicians in the use of steroids during clinical trials. Further, a recent report also demonstrated that the severity of a particular relapse did not have a reliable impact on progression on the EDSS [Bejaoui and Rolak, 2010]. Thus, measuring the severity of study relapses, as an outcome measure, is of uncertain utility or added benefit.

Relapse rate has been the cornerstone of therapeutic trials in MS as a tangible measure of inflammatory disease activity. However, there are some concerns and limitations in depending on relapse frequency as a clinical outcome measure in MS. The association between MS relapse and long-term disability is uncertain, and in some cases reported to be weak-to-moderate [Confavreux *et al.* 2000; Weinshenker *et al.* 1989a]. Subclinical change on MRI and insidious changes in disease progression between relapses likely contribute to MS disability progression which is not captured by measuring relapse rates alone. As patients progress over time the number of relapses appears to decrease [Tremlett *et al.* 2009]. For patients experiencing progressive disease, either primary or secondary, other clinical measures are needed. Recent trials have suggested that the overall relapse rate of the MS population is decreasing over time [Achiron and Fredrikson, 2009]. There are also periods of relapse quiescence [Tremlett *et al.* 2009] and possible 'regression to the mean' during on-study treatment, requiring larger numbers of subjects or longer studies to demonstrate treatment effects. These limitations in relapse rate assessment have lead to an increased interest in the use of MRI as an alternate measure for MS disease activity and which has gained popularity, particularly in short-term phase II trials of potential MS therapies. However, the relationship between the clinical and subclinical changes on MRI and long-term MS-related disability remains unclear and it has recently been called into question whether MRI offers additional information beyond our current clinical outcome measures of relapse rate and EDSS [Daumer *et al.* 2009; Sormani *et al.* 2009b]. Taking a different approach to understanding the relationship between MRI and clinical outcomes, a recent meta-analysis reported that the treatment effect on MRI and on relapse rate are highly correlated. There was a suggestion that, although the direct association between MRI and relapse rate or disability has heretofore been limited, treatment effects demonstrate a similar impact on MRI activity and relapse rate concurrently [Sormani *et al.* 2009a].

Expanded Disability Status Scale

The first Disability Status Scale was introduced by Kurtzke in 1955. In 1961, this was later expanded into eight functional systems [Kurtzke, 1961]. Functional systems include: vision, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, mental (cerebral) and ambulation (500-m walk). In 1983 the Expanded Disability Status Scale (EDSS), a 10-point scale of disease severity ranging from 0 (no disability) to 10 (death from MS) was published [Kurtzke, 1983]. In the low range, 0–3.5, the EDSS is based on the modest-to-moderate change in one or more of the functional systems. Above 4.0, scoring is based primarily on gait dysfunction. From 6.0–7.5, disability is exclusively dependent on walking function: use of aids (unilateral 6.0 and bilateral 6.5) and ambulation distance. EDSS of 8.0 marks loss of ambulation. Upper extremity function distinguishes 8–9, bulbar function 9–9.5, and death defines a score of 10. The EDSS has been used for over 20 years as a clinical outcome measure of MS disease progression and is commonly the standard that other outcome measures are compared against.

Five of the EDSS functional system scores are based on the neurological exam, which makes the measure familiar and comfortable for most neurologists. Owing to its common use in research over the years, most MS neurologists understand what a given EDSS score 'looks like' and it is easy to compare between patients cross-sectionally. Despite its acceptance and extensive use in MS research, the EDSS has several limitations as a clinical outcome measure of MS disease progression. The EDSS is an ordinal measure and differences between each level are not comparable. That is, moving from EDSS 1.0 to 2.0 is very different to the transition from 6.0 to 7.0. This complicates the statistical analysis of the outcome measure; because of the

nonlinearity of the scale, comparing mean changes across groups is not appropriate when using the EDSS. Also due to the ordinal nature of the EDSS, time spent at each step varies significantly, with the least amount of time spent in the mid range between 3.0 and 6.0 [Weinshenker *et al.* 1991, 1989b]. Therefore, rate of progression on the EDSS during a 2-year clinical trial will depend on EDSS levels at trial entry. If this is not balanced across treatment arms, spurious results on EDSS worsening may occur. Indeed, assessments of the responsiveness or sensitivity to change of the EDSS are disappointing overall and appear weakest at the lowest and highest range of the scale [van Winsen *et al.* 2010; Rudick *et al.* 2009a; Kragt *et al.* 2008; Hobart *et al.* 2003, 2000; Schwid *et al.* 2000b; Sharrack *et al.* 1999]. Change in EDSS is the standard definition for disease progression in clinical trials; however, the definition of disease progression measured by EDSS varies throughout the literature. The most common definition is a 1.0 step increase for individuals with an overall EDSS $\leq$ 6.0 confirmed at 3 months. Despite the widespread use and acceptance of this definition of disease progression by EDSS, the validity of this approach is uncertain and the optimal change in EDSS that predicts long-term permanent sustained disability remains undefined [Ebers *et al.* 2008; Kragt *et al.* 2006a]. A recent longitudinal follow up of patients in a phase III trial suggest that worsening on EDSS of $\geq$ 1.0 point confirmed at 6 months is predictive of clinically significant disability at 8 years [Rudick *et al.* 2010]. This work will provide guidance for future study criteria for short-term change in EDSS as a measure of progression.

There are several examples in the literature of statistical extrapolations and manipulations of the EDSS which aim to improve its functionality and long-term predictability and utility. These include use of Markov transitional models [Gauthier *et al.* 2007], predictive longitudinal disability curves [Achiron *et al.* 2003], and evaluation of area under the curve generated from all EDSS scores (Integrated Disability Status Scale) [Liu *et al.* 1998]. The Multiple Sclerosis Severity Scale (MSSS) is another approach to improve on the EDSS in characterizing disease severity and disability progression [Narayana *et al.* 2005]. The MSSS is a probabilistic method that assigns a disease severity score by integrating the EDSS and duration of disease. This makes intuitive sense; two patients with moderate disability, one with disease for 3 years and the other 25 years, appear to represent different expressions of disease severity and anticipated progression trajectories over time. While promising, the utility of the MSSS in comparing groups of MS patients over time remains uncertain. The MSSS retains the limitations of the EDSS; the advantages of integrating disease duration will require further exploration. While the EDSS is the current gold-standard measure of MS disease progression, ongoing work to optimize this clinical outcome measure will be important and extrapolations and transformations of the EDSS as described above hold promise in helping us understand the long-term impact of short-term changes in EDSS.

MS functional composite

Recognizing the need for an improved clinical outcome measure in MS, the National Multiple Sclerosis Society (NMSS) sponsored an international workshop entitled 'Outcomes Assessment in Multiple Sclerosis Clinical Trials' [Rudick *et al.* 1996]. The workshop participants concluded that new clinical outcome measures were needed to reliably reflect progression of disease and clinical change. Further, the desired measure would demonstrate high reliability, validity, and be sensitive to change over short time intervals. In addition, the desired measure would be practical and cost effective as a clinical outcome assessment tool for MS clinical trials. Following this workshop, a task force was convened. The task force recommended the MSFC as a new clinical outcome measure for MS clinical trials [Rudick *et al.* 2002, 1997; Cutter *et al.* 1999]. The MSFC is a composite measure that includes: measurement of ambulation (Timed 25-Foot Walk, [T25FW]); arm function (Nine-Hole Peg Test [9HPT]); and cognition (Paced Auditory Serial Addition Test [PASAT]) [Rudick *et al.* 1997]. The component scores are transformed into *z*-scores by standardizing to a reference population, and the individual *z*-scores are averaged to create the composite MSFC. Use of component *z*-scores allow for transformation of T25FW and 9HPT scores so that a decrease represents worsening. There are several advantages to the MSFC over the EDSS. The MSFC can be obtained in approximately 10 minutes by a trained technician, making it very economical for clinical trial applications. The MSFC includes three critical elements of MS disability, importantly measuring cognition, a facet of MS-related disability not captured by the EDSS. The component and sum scores provide continuous data which allows for parametric analysis.

Transformation to a *z*-score allows comparison of an individual to the average population (internal or external reference population). The MSFC has been validated against the EDSS, MRI and quality of life measures demonstrating its validity, reliability and sensitivity to change [Rudick *et al.* 2009a; Pascual *et al.* 2008; Cohen *et al.* 2001, 2000; Kalkers *et al.* 2001, 2000; Miller *et al.* 2000; Cutter *et al.* 1999].

The MSFC was first used as a primary outcome measure in a placebo-controlled trial of interferon beta-1a in SPMS patients [Cohen *et al.* 2002]. The learning effects noted for the MSFC were attenuated in this study by three prebaseline test sessions to achieve a stable baseline. In this trial, the treatment arm demonstrated a 40% reduction in MSFC change relative to placebo. This change was driven by the 9HPT and PASAT components. The study demonstrated that the MSFC is informative in a clinical trial setting. Interestingly, there was no significant treatment effect on EDSS. This suggests that the MSFC is more sensitive than EDSS in demonstrating change. Despite this early success with the MSFC and its advantages over the EDSS, its acceptance and utilization as a primary outcome measure have been limited. The transformation of data to a *z*-score, and the interpretation of a statistically significant benefit have proved to be important barriers. While statistically useful, the *z*-score is not intuitive. Further, the dependence on a reference population for *z*-score calculation anchored the results to the characteristics of that specific reference population, making comparisons across studies difficult.

The most recent application of the MSFC in clinical trials was in the fampridine (4-AP, Ampyra) study. The primary outcome measure for the phase III trial was on-drug T25FW performance compared with baseline. Treatment responders were defined as subjects with improved speed in three out of four on-drug trials compared with baseline [Hobart *et al.* 2003]. The decision to use this performance-based definition of responder may have been due to the lack of a consensus definition of clinically important change in the MSFC composite or subscores. Research suggests defining a meaningful cut point may improve the responsiveness and predictive value of the MSFC [Kragt *et al.* 2008]. This has been an ongoing area of research and there have been several explorations of MSFC scoring to define a meaningful change [Rudick *et al.* 2009b; Kragt *et al.* 2006b; Schwid *et al.* 2002].

The MSFC is an important and valuable addition as an outcome measure in MS research. As anticipated by the NMSS Task Force, it has continued to evolve and may undergo further changes in the future. These include addition of a visual component, and substitution of an alternative cognitive measure, as the PASAT is prone to prominent learning effects, and patients generally find completing the PASAT distressing [Drake *et al.* 2010; Brochet *et al.* 2008].

Possible clinical outcome measures

Relapse rate, EDSS, and MSFC each have strengths and some weakness. The optimal MS disease progression outcome measure is still not clearly defined. We discuss two promising outcome measures that might augment current MS outcome measures. These two measures, the six-minute walk (6MW) and accelerometry, both focus on ambulation. Loss of mobility is ultimately a ubiquitous feature of MS disability. In fact, gait impairment has been demonstrated in the earliest stages of the disease, prior to any measured disability using the EDSS [Martin *et al.* 2006]. This suggests that measurement of walking impairment could be a subtle and early sign of disability. Walking has also been reported by patients to be one of the most valuable bodily functions [Heesen *et al.* 2008]. Therefore, the ability to measure early impairment and small changes in walking function during disease progression is an important aspect of an MS outcome measure. There are several possible measures of ambulation that have been utilized in the MS research including the Ambulatory index, EDSS 500-m walk, T25FW, 100-m walk, 6MW, and accelerometry. Among these, the EDSS 500-m walk and T25FW are the most utilized. Previous research has suggested that continuous ambulatory measures are more precise than ordinal measures such as the Ambulatory index [Schwid *et al.* 1997].

As an ordinal measure, the EDSS is insensitive to change over time especially at the high end of the scale ($\geq$4.0) where marked loss in ambulatory function is required for a half- or one-step increase in the scale. Even in fully ambulatory patients, the EDSS has proved to have limited sensitivity to change [van Winsen *et al.* 2010; Schwid *et al.* 2000a]. The ambulatory component

of the EDSS is a 500-m walk, which is transformed into ordinal data when used to calculate a total disability score. The 500-m walk has poor reliability (interclass correlation = 0.36 in MS and 0.21 in controls) [Schwid *et al.* 1999]. The 500-m walk is also logistically difficult because there is no time limit and patients can continue to attempt to walk until they feel they are no longer able.

The T25FW appears to be more sensitive to change when compared with the EDSS [Schwid *et al.* 2002]. However, it also appears to suffer from poor responsiveness in mild-to-moderately impaired ambulatory MS subjects (EDSS 3.0–6.5) with an estimated effect size of 0.3–0.4 [Hobart *et al.* 2003; Schwid *et al.* 2000a]. The T25FW also appears to have reduced sensitivity in the lower range of the EDSS (<4.0), perhaps reflecting a floor effect in these patients [van Winsen *et al.* 2010]. These data suggest that additional measures of walking impairment are needed. There is an emerging body of evidence indicating that the 6MW and accelerometry represent novel candidate markers of ambulatory impairments in persons with MS which may provide advantages over other available ambulatory measures.

Six-minute walk

The 6MW was first validated in 1982 and has been widely used in the cardiopulmonary literature [Butland *et al.* 1982]. Over the last 7 years, it has been used increasingly in neurological populations. The 6MW has been used in studies of stroke [Daly *et al.* 2006; Ada *et al.* 2003; Dean *et al.* 2000; Duncan *et al.* 2000], Parkinson's disease [Garber and Friedman, 2003], muscular dystrophy [Kierkegaard and Tollbäck, 2007], spinal muscular atrophy [Montes *et al.* 2010], and MS [Gijbels *et al.* 2010; Goldman *et al.* 2008; Paltamaa *et al.* 2008, 2007; Savci *et al.* 2005; Chetta *et al.* 2004]. The 6MW has been validated as a measure of ambulatory capacity in persons with MS [Goldman *et al.* 2008]. Indeed, the distance traveled during the 6MW has consistently differed between persons with MS and controls and has correlated strongly with the EDSS, T25FW, and Multiple Sclerosis Walking Scale-12 (MSWS-12) scores in persons with MS [Goldman *et al.* 2008; Savci *et al.* 2005]. The 6MW offers several improvements over the 500-m walk component of the EDSS including excellent reliability, robustness as a continuous outcome measure, and time limitation (6 minutes). The 6MW has also demonstrated improved precision compared with the T25FW in defining MS-related disability [Goldman *et al.* 2008]. The 6MW is well tolerated, even in MS subjects with severe walking disability [Goldman *et al.* 2008].

A 2-year longitudinal study in Finland showed that shorter distance walked on the 6MW test was one the most significant predictors of perceived difficulties or dependence in activities in daily living (ADL) performance [Paltamaa *et al.* 2007]. This same group reported the 6MW was responsive to change both measured by the EDSS (area under the curve [AUC] = 0.76) and patient perception (AUC = 0.76) [Paltamaa *et al.* 2008]. A recent study assessing habitual walking performance (HWP), i.e. ambulation in a customary living environment, compared several walking outcome measures including T25FW and 6MW [Gijbels *et al.* 2010]. The authors report the 6MW was most predictive of HWP in MS subjects and in the mild MS subgroup (EDSS 1.5–4.0). In the moderate MS subject group (EDSS 4.0–6.5), the 6MW outperformed T25FW as a predictive measure of habitual walking performance. The authors conclude that the inclusion of prolonged walking tests is needed in MS clinical research to better reflect community walking performance.

The 6MW is a promising measure of walking performance in MS. It appears to identify changes in mild MS subjects, where the 500-m walk and T25FW are less sensitive in detecting change. The 6MW has been demonstrated to reliably predict walking ability in one's customary living environment and, as such, appears to be an important tool in clinical research that reflects real-life mobility. Limited studies have demonstrated that the 6MW is responsive to change across a range of ambulatory MS patients. Additional research is needed to validate 6MW performance longitudinally and verify its sensitivity to change. Further assessment of 6MW performance in more disabled MS subjects will clarify its value in the progressive stage of the disease.

Accelerometry

Accelerometers are motion sensors that measure the applied acceleration acting along a sensitive axis. This measurement of acceleration is typically accomplished through a piezoelectric bender element that has a small mass located on the end of a cantilevered arm and that

responds to acceleration. Accelerometers can be applied for the measurement of human movements, and the placement close to the center of mass is typical for the measurement of whole-body movements, such as occur during walking. There has been an increasing recognition of the potential value of commercially available accelerometers for measuring mobility or walking impairment in neurological populations [Pearson *et al.* 2004] including persons with MS [Weikert *et al.* 2010; Snook *et al.* 2009]. The ActiGraph model 7164 accelerometer is small, lightweight, and powered by a replaceable lithium cell battery. This accelerometer provides a continuous measurement that can be used for prolonged periods (i.e. days, weeks, and months) with minimal interference on normal patterns of life, and the signal can be inspected for patient compliance.

Researchers have provided preliminary evidence that the signal from the ActiGraph model 7164 accelerometer when worn on a belt around the waist might measure walking impairments in persons with MS. This application is based on the assumptions that an accelerometer worn around the waist (i.e. center of mass) will capture the signal associated with walking. Walking is a primary and significant form of movement undertaken by ambulatory persons with MS, and the intensity, duration, and frequency of walking are directly proportionate to impairments in walking parameters (e.g. speed, stride length and cadence, and double support time). The evidence indicates that the average of total movements counts per day across a seven-day period is correlated with MSWS-12 scores, EDSS, Performance Scale mobility subscale scores, and the Symptom Inventory [Motl *et al.* 2009a, 2009b, 2008; Motl and Snook, 2008]. Our unpublished data indicate that the average of total movements counts from an ActiGraph model 7164 accelerometer worn around the waist is also well correlated with 6MW distance ($r = 0.52$ and 0.78), the oxygen cost of walking ($r = -0.54$), and global spatiotemporal measure of gait from the GAITRite gait mat ($r = -0.57$). We finally note that the metric of total daily movement counts was significantly reduced over a 6-month period in a longitudinal, observational study of persons with mild MS, whereas self-report measures of symptomatology and function did not change over that same period [Motl and McAuley, 2009].

Additional research is clearly necessary for establishing the relative validity and responsiveness of accelerometry versus biometric, clinical, kinematic, performance, physiological, and self-reported measures for assessing changes in walking impairments with disease progression (i.e. worsening MS) or disease activity (i.e. acute relapse) in persons with MS. We further believe that there is merit in examining the value of including accelerometers in clinical trials of disease-modifying and symptomatic agents as this measure might provide unique information on impairments in walking that occur in the context of real life. The added value of accelerometry as an outcome measure of walking impairments in MS will only be witnessed through future research applications, and such applications might come with tremendous success or failure.

Summary

MS therapeutics is a quickly advancing field which requires sensitive clinical outcome measures that can detect small changes in disability that reliably reflect long-term changes in sustained disease progression. Current outcome measures have individual strengths and weakness. There is a clear association between the MS relapse rate and changes in both the EDSS and MSFC over time. The challenges to measuring MS disease progression are multifaceted and emerging research suggests that the current measures may perform best at different stages of the disease. New ambulatory outcome measures may offer additional sensitivity and augment the EDSS and MSFC over the range of MS-related disability. A single MS outcome measure of sustained disease progression may remain elusive. Rather, an integration of current and new outcome measures may be appropriate and utilization of different measures depending on the MS population and stage of the disease may be preferred. Finally, researchers need to be cautious of the trappings of validating new outcomes measure against the EDSS, which these new measure are intended to improve upon.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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