Exercise in Patients with Multiple Sclerosis

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Abstract

Exercise is one of the best rehabilitation approaches for managing symptoms, restoring function, optimizing quality of life, promoting wellness, and boosting participation in activities of daily living among persons with multiple sclerosis (MS). However, persons with MS engage in low levels of health-promoting physical activity, and this has not changed over the past 25 years, despite substantial expansion of the evidence-base. Such a conundrum can be addressed by identifying “limitations between research and practice” that prevent exercise promotion through the patient-provider interaction. The primary limitations that prevent exercise promotion include the inadequate quality and scope of existing evidence, incomplete understanding of mechanisms supporting beneficial effects of exercise in multiple sclerosis, and lack of a conceptual framework and toolkit for translating the evidence into practice. Future research that addresses those limitations will be essential for better informing decisions on the inclusion of exercise in the clinical care of people with MS.

Introduction

Multiple sclerosis (MS) is typically described as a chronic, immune-mediated disease of the central nervous system (CNS) with an increasing recognition of neurodegenerative processes in its pathogenesis.[1] The disease activity and resulting damage manifest as symptoms (e.g., fatigue and depression) and dysfunction (e.g., walking and cognition) that compromise quality of life (QOL) and participation. MS is typically treated through disease modifying drugs that target immunological signaling proteins (e.g., interferons, cytokines) and/or populations of immune cells (e.g., lymphocytes). This approach substantially controls inflammatory activity, but not neurodegenerative processes, so persons with MS still experience residual symptoms and dysfunction, as there is no cure for the disease.

Participation in physical activity, particularly exercise training (see standard definitions[2] in Panel 1), increasingly has been recommended for managing symptoms, restoring function, optimizing QOL, promoting wellness, and boosting participation in activities of daily living in MS.[3] To that end, exercise is one of the best rehabilitation approaches for addressing the multi-faceted problems of MS. Nevertheless, persons with MS engage in low levels of health-promoting physical activity, and this has not changed over the past 25 years, despite substantial expansion of the evidence-base. The presents a conundrum – exercise and physical activity offer wide-ranging benefits, but people with MS are not sufficiently physically active.

This Personal View paper is derived from an International team of rehabilitation researchers and/or clinicians in MS and adopts the vantage point that the conundrum with exercise behavior in MS (i.e., lack of broad participation by people with MS despite evidence of meaningful benefits) can be addressed through healthcare providers, if we ameliorate keys limitations in the body of research. Overcoming the limitations and narrowing the gap between research and clinical practice is both timely and important considering the impact of the aforementioned conundrum with exercise and physical activity in persons with MS. We focus on three broad categories of limitations, with examples and possible solutions, that represent the substantive content of this paper. If these key limitations are addressed, healthcare providers would be positioned and empowered to tackle the barriers that impede knowledge translation regarding exercise as part of comprehensive care in people with MS.

Effects of Exercise in MS

There has been an increasing amount of research examining the effects of exercise training and participation in physical activity on consequences of MS. Collectively, the majority of exercise research in MS has focused on outcomes involving physical fitness, walking mobility, balance, cognition, fatigue, depressive symptoms, and QOL consistent with the ordering of constructs within the International Classification of Function model of MS pathogenesis[3]; this is summarised in Table 1 along with indices of overall methodological quality for studies included in the meta-analyses, Cochrane reviews, or systematic reviews. Of note, the exercise training in the existing body of research typically has taken place in supervised, laboratory-based settings rather than non-supervised, home-based or community settings.

Physical Fitness. One systematic review and two meta-analyses have summarized the effects of exercise training on physical fitness outcomes in persons with MS.[4-6] This is critical considering the deleterious effects of MS-related physiological deconditioning.[7] There is evidence for small improvements in lower-extremity muscle strength (e.g., d=0.27) following resistance exercise training,[6] and moderate-sized improvements in cardiorespiratory fitness (e.g., d=0.47-0.63) following aerobic exercise training[5,6] in this population (Table 1). The improvement in aerobic fitness is seemingly large enough for secondary health benefits and therefore considered clinically meaningful.[5] Those systematic reviews/meta-analyses have highlighted that many studies are underpowered; lack blinding of participants, therapists, and assessors; do not perform intent-to-treat analyses; and often involve samples with primarily relapsing-remitting MS.[4-6]

Walking Mobility. Over the past five years, there have been two meta-analyses examining the effects of exercise training on walking mobility outcomes in persons with MS.[8,9] Overall, the studies demonstrated small (e.g., *d*=0.25)[9], but beneficial (and clinically-meaningful) effects of exercise training on walking speed and walking endurance. Such effects were relatively homogeneous across modalities of exercise training (i.e., aerobic versus resistance). The recent meta-analyses[8,9] confirmed the results of an earlier meta-analysis[10] that reported small, beneficial effects of exercise on walking outcomes in MS. However, the recent meta-analyses have reported that there is substantial heterogeneity of exercise training protocols, and this limits the ability of clinicians to prescribe a specific exercise program for selectively improving mobility in MS.[8,9]

Balance. To date, there has been one meta-analysis of exercise training effects on balance outcomes in persons with MS.[11] That meta-analysis concluded that exercise training has a small (e.g., *d*=0.34), but statistically significant beneficial effect on balance outcomes in this population. The meta-analysis highlighted that most studies were small and underpowered for detecting meaningful balance improvements, and existing randomized controlled trials did not adequately report intervention details or randomization procedures for enhancing the reproducibility of such research.[11] Interestingly, results from a recent series of preliminary studies have supported balance exercise training for improving metrics of postural control and possibly cerebellar white and grey matter integrity (i.e., inducing neuroplasticity) in persons with MS.[12,13]

Cognition. There has been one comprehensive systematic review examining the effects of exercise, physical activity, and physical fitness on cognitive outcomes in persons with MS;[14] no focused meta-analyses are available in this area. The systematic review summarised that there is not clear evidence regarding a beneficial effect of exercise training on cognition in persons with MS. The current state of the evidence might be attributable to several methodological shortcomings of exercise trials (i.e., Class I and II trials), for example, lack of inclusion of cognition as a primary outcome, poorly-designed exercise interventions, and lack of inclusion of cognitively-impaired persons with MS.[14] We do note that recent preliminary evidence supports the beneficial effects of physical activity and exercise training on cognition in this population.[15-17]

Fatigue. Two meta-analyses[18,19] and one Cochrane review[20] have examined the overall effects of exercise on fatigue outcomes in persons with MS. These quantitative syntheses have reported overall statistically significant and moderate-sized reductions in fatigue (e.g., *d*=0.45-0.57) following exercise training in persons with MS. Interestingly, one meta-analysis reported that the overall effects were relatively consistent across studies,[18] whereas the Cochrane review reported overall heterogeneous effects of exercise interventions on fatigue outcomes.[20] It is of considerable importance that all three reviews[18-20] noted the lack of pre-screening participants for severe MS-related fatigue, such that the trials did not examine exercise as a possible treatment for fatigue in MS. Other limitations related to the state of the literature include underpowered studies, selective reporting of outcomes, and the broad range of exercise interventions across studies.[18-20]

Depressive Symptoms. The search strategy and selection criteria yielded three meta-analyses regarding the effects of exercise training on depressive symptoms in persons with MS.[21-23] The meta-analyses reported small (e.g., *d*=0.28-0.37), but consistent beneficial effects of exercise on depressive symptoms in this population (see Table 1). Interestingly, one meta-analysis reported that the benefits of exercise on depressive outcomes might be particularly large if the intervention dose meets published physical activity guidelines.[23] Of note, as is the case for the body of literature on exercise effects on fatigue in MS, there is an overall lack of pre-screening for individuals with elevated depressive symptomology or major depressive disorder. Thus, the state of the literature can only report on the effects of exercise on depressive symptoms, as opposed to exercise as a possible treatment for major depressive disorder in MS.[21-23]

QOL. There has been one recent (i.e., since 2012) systematic review regarding the effects of exercise training on QOL outcomes in persons with MS.[24] The authors of that systematic review reported insufficient evidence for a conclusion regarding the effects of exercise on QOL. This is not consistent with the results of an early meta-analysis[25] that reported small (e.g., d=0.23), but statistically significant improvements in QOL in this population. Importantly, several issues that might contribute to the overall mixed evidence involve the lack of consistent outcome measures across studies (i.e., general versus disease-specific QOL outcomes; use of composite QOL outcomes versus subscales).[24]

Other recent studies of exercise in persons with MS indicate that there may be additional benefits on structures within the CNS (e.g., hippocampus),[26,27] sleep quality,[28] and cardiovascular/metabolic cormorbidity.[29,30] Exercise further has been associated with reduced rates of MS relapses[31,32] and slowed disability progression.[33] The safety profile (i.e., occurrence of adverse and serious adverse events) in MS is comparable with the general population of adults.[31] This underscores that participation in exercise is safe and can yield many benefits for persons living with MS (i.e., pleiotropic effects), and exercise has been recognized as a primary approach for restoring physical function[34] and perhaps even modifying the disease.[35,36] The evidence base has yielded guidelines for prescribing exercise behavior in persons with MS who have mild or moderate neurological disability (*www.csep.ca/CMFiles/Guidelines/specialpops/CSEP_MS_PAGuidelines_adults_en.pdf*)[24,37] that can be implemented within comprehensive MS care.[38]

Factors Affecting Exercise Participation in MS

The proliferating body of evidence indicates small-to-moderate effects of exercise training on fitness, symptoms, and function in persons with MS. The problem, however, is that the majority of people with MS do not engage in appropriate amounts of health-promoting physical activity or exercise. There is consistent evidence from meta-analyses that people with MS engage in substantially less physical activity than healthy controls from the general population but similar to those with other chronic diseases.[39,40] There is additional evidence from waist-worn accelerometry that persons with MS engage in reduced amounts of moderate-to-vigorous physical activity (MVPA) compared with the general population,[41] and physical activity levels decrease over time as the disease develops.[42] The data further suggest that fewer than 20% of people with MS from the U.S. engage in recommended amounts of MVPA necessary for health benefits compared with 40% of healthy, control samples;[41,43] the rate of physical activity even is low for persons with mild MS who do not have significant disability.[41] We further note that the difference in physical activity levels between MS and healthy controls has not changed over the past 25 years,[39,40] even though the evidence base for MS-related benefits has expanded considerably over the past 10 years.[44]

There is an obvious disconnect between evidence of benefits and rates of participation, possibly indicating lack of, or inefficient promotion of, exercise adoption and maintenance in this population. This underscores the complexity of health behavior change in MS, and the importance of identifying opportunities and approaches that can facilitate long-term behavior change (e.g., exercise interventions that include behavioral components in MS). The disconnect presents a conundrum – exercise and physical activity offer wide-ranging benefits, but people with MS are not sufficiently physically active. That is, exercise cannot be effective if people do not do it. This disconnect is critically important, as the chasm between benefits and participation may be even larger in MS than the general population, and the roles of exercise and physical activity might be most important in a disease wherein people are facing functional declines and other outcomes.[45] The conundrum is seemingly not linked with compliance regarding specific exercise programs, as over 80% of people with MS who are enrolled in randomized controlled trials (RCTs) of structured, supervised exercise training complete the prescribed regimen.[31]

There has been considerable interest in identifying determinants (i.e., variables that correlate with behavior and that might serve as targets of interventions for changing behavior) of exercise and physical activity behavior in MS.[46,47] The rate of physical activity participation in MS may reflect physical limitations associated with ambulatory disability, symptoms of MS (e.g., depression, fatigue), environmental barriers (e.g., lack of access to facilities), and/or psychosocial factors related to behavior change (e.g., self-monitoring, self-efficacy, goal setting, social support) as summarized in a systematic review.[46] There has been further interest in the application of behavior change theory for studying determinants of physical activity behavior in MS, and this body of research has largely focused on variables from social-cognitive theory (SCT).[47,48] Of note, SCT recognizes the interaction between the person and environment (physical and social) when considering behavior change, and this underscores the importance of identifying environmental facilitators that permit successful application of programs for behavior change among persons with MS.

We propose that the underutilisation of physical activity in people with MS, despite supporting evidence of its benefits, can be overcome by ameliorating three key limitations in exercise research: quality and scope of existing evidence, mechanisms supporting beneficial effects of exercise in multiple sclerosis, and conceptual framework and toolkit for translating the evidence.

Quality and Scope of Existing Evidence

There is evidence from NIH-defined Phase I and II clinical trials indicating that exercise has substantial benefit for those with MS.[49] Yet, this evidence has limitations for specific indications that limit translation of knowledge into clinical practice (see Table 1). First of all, there are no effectiveness trials (i.e., NIH-defined Phase III clinical trials) of exercise and its benefits in MS, and few studies focusing on the dose-response association between exercise training parameters (e.g., intensity and/or frequency) and MS outcomes.[50,51] Another limitation in current research on outcomes of exercise training is derived from samples that are not prescreened for the presence of a specific symptom or dysfunction associated with MS. For example, there are over 20 RCTs indicating that exercise training improves measures of fatigue (e.g., d=0.45)[18] and/or depressive (e.g., d=0.36)[21] symptoms. The two papers that included systematic reviews of inclusion criteria and sample characteristics indicated that few, if any, of the studies actually included persons with severe or impactful fatigue and clinical depressive symptomology or even major depressive disorder. [20,22] This is important considering the high prevalence and burden of fatigue and depression in MS[52] that further might influence the high rates of physical inactivity in this population.[53] There may be variability in outcomes of exercise training by MS phenotypes, yet such heterogeneity has not been systematically examined in the existing body of research. Indeed, the existing research has often included samples of persons who have relapsing-remitting MS (RRMS) and/or mild or moderate MS-related disability;[18,20,49] this research has further focused on relatively healthy samples without comorbid conditions that are common in MS.[54] The cumulative evidence has yielded publicly-available guidelines for exercise training in adults with RRMS who have mild or moderate disability (Table 2).[24,37] The body of research is substantially weaker when focusing on progressive forms of MS and those with severe disability.[55-57] We note, in particular, that reviews of the literature report insufficient evidence for conclusions regarding the benefits of exercise in progressive forms of MS and those with severe disability.[55-57] This is particularly relevant, given that persons with progressive MS who have severe ambulatory disability are significantly less physically active than persons with RRMS.[41] This cohort represents a segment of the MS population who might benefit the most from exercise training.[49]

Alarmingly, the evidence is not sufficiently developed in scope whereby providers would have confidence in applying exercise training for managing symptomatic and functional outcomes in progressive forms of MS and persons with severe disability status.[56] The evidence further is not substantial enough for developing evidence-based prescriptive guidelines in these segments of the MS population. This is an enormous limitation that must be overcome, as most disease modifying drugs are not approved for progressive MS and/or are ineffective in later stages of RRMS (e.g., Expanded Disability Status Scale score of 4.0 or greater).[58,59] The focus on the benefits of exercise training among these segments of the MS population is sorely needed for knowledge translation within clinical practice. Future research must target and recruit samples of participants *a priori* who present with an actual disease-specific problem when studying the benefits of exercise in MS. This is key for knowledge translation whereby providers can prescribe exercise for a specific problem in person with MS.

There is a noteworthy absence of clearly-defined primary endpoints, as illustrated in RCTs of exercise training and depression wherein only 1 of 12 studies identified depression as a primary endpoint.[22] This is a significant problem as clinicians are unlikely to recommend or prescribe exercise for treating a significant and specific problem – if the evidence does not support such a specific application and indication. This problem may further result in the effects of exercise being underestimated (i.e., floor effects) in RCTs, and warrants further study. There further is a lack of consensus regarding a problem-specific set of validated, core outcomes for inclusion in exercise trials and this might serve as a roadblock in the translational pipeline. There is an increasing emphasis on clinically meaningful effects of interventions in MS, and yet few RCTs of exercise training properly reflect on whether the changes in focal outcomes signal an improvement that has value in a patient's life (i.e., clinical relevance based on benchmarks of meaningful change). The aforementioned problems should be addressed in future research geared towards strengthening the quality of the knowledge base for translation into clinical practice.

Numerous other problems beset the quality of the existing research. For example, there is very limited evidence regarding the durability or sustainability of exercise effects on consequences of MS; this was highlighted by a seminal Cochrane Review over 10 years ago,[60] and continues to be a major limitation.[49] The lack of knowledge regarding the sustainability of exercise effects on fitness, symptoms, and function in this population brings into question whether or not exercise can exert a meaningful disease-modifying change in those outcomes. The provision of long-term follow-up outcomes related to activities of daily living in future exercise trials might serve to instill confidence in providers for promotion of appropriate exercise programs in MS patients. Other problems include underpowered studies[21] with small sample sizes (e.g., mean sample size in RCTs = 50, range of 14-130),[44] and many studies do not include blinded assessors or intent-to-treat analyses[18,20,22] nor focus on metrics of Reach (e.g., number, proportion, or representativeness of those who participate), Effectiveness (e.g., change in appropriate outcomes including QOL), Adoption (e.g., number, proportion, or representativeness of settings/clinicians who participate), Implementation (e.g., extent, time, and costs of consistent program delivery), and Maintenance (e.g., long-term effects and attrition) (RE-AIM principles)[61] when designing and evaluating trials.

There are other issues that limit the scope of the available research involving exercise and MS. For example, the majority of people with RRMS are on a disease modifying drug, yet such information is not systematically collected, reported, and/or statistically accounted for in RCTs of exercise training; there are similar problems regarding symptomatic agents and other rehabilitation therapies besides exercise. This presents a problem, as we do not have a clear understanding of the benefits of exercise in the context of disease modifying drug usage for consideration by providers in the promotion on exercise among people with MS. There is as of yet no consideration of the role of exercise training as an add-on or stepped-care therapy in MS. For example, cognitive behavior therapy is a common approach for managing depression in MS, but it alone is not always effective[62] and exercise could be added as a stepped-care approach for therapy. There is very little known about exercise within the context of relapses.[63] For example, should a patient discontinue exercise during a relapse for safety? When and how should exercise be reinitiated after resolution of a relapse and is exercise only suitable after certain types of relapses? The aforementioned problems should be the focus of future research for broadening the scope of the knowledge base for translation into clinical practice. Indeed, high quality research in this area might provide a stronger evidence base whereby providers would be more likely to prescribe exercise along with adjuvant pharmacological or other rehabilitative therapies for improving function in this population.

One final issue associated with the quality and scope of existing research is a glaring lack of knowledge regarding how to maximize adherence and compliance with exercise training programs.[31,44] Future research studies might consider integrating approaches based on behavior change theories such as SCT within exercise training programs for maximizing adherence/compliance and long-term maintenance. Such approaches could further strengthen the patient-provider interaction by providing guidance regarding how patients can optimally initiate and maintain physical activity behavior over time for realizing its possible benefits.

Mechanisms Supporting Beneficial Effects of Exercise in MS

The vast majority of research on outcomes of exercise training has focused on symptoms, functions, and QOL, whereas there is limited research on the mechanisms of exercise training effects in MS. That is, we know that exercise exerts many benefits in MS, but we do not know how or why. The examination of biological factors for exercise training effects in this population is critical for increasing the confidence of healthcare providers for promoting exercise in MS patients. Healthcare providers still have doubts about the biomedical efficacy of exercise in MS, and understanding the mechanisms of exercise effects is important for convincing providers about the biological basis for exercise effects in MS. There are an increasing number of studies examining neural and molecular mechanisms of exercise and physical activity in animal models of MS (e.g., experimental autoimmune encephalomyelitis or EAE).[64] However, such animal studies are often inconclusive, difficult to interpret, and might undermine the promotion of exercise in persons with MS by providers who are skeptical of the actual clinical translation of the animal work.

There have been some efforts toward studying mechanisms of exercise effects in people with MS by focusing on immune cells and neurotrophic factors in peripheral blood samples;[3] the assumption is that samples taken from the periphery reflect ongoing pathophysiology in the CNS. The existing research, however, provides a conflicting picture of changes in immune and neurotrophic factors with exercise in humans with MS,[3] and further does not consider that MS is typically an acute, episodic disease (e.g., RRMS) that involves intermittent bursts of inflammation, although there is some ongoing, chronic inflammation.[1] To that end, future clinical trials might overcome the limitations by collecting peripheral blood samples with acute bouts of exercise during a relapse (i.e., period wherein there is disruption of the blood-brain barrier allowing lymphocyte migration into CNS) or cerebral spinal fluid with long-term exercise training.

There is emerging evidence supporting that exercise may promote neuroplasticity in persons with MS. Several cross-sectional studies suggest that aerobic fitness/physical activity are positively associated with volumes of subcortical grey matter structures (e.g., hippocampus and basal ganglia) in MS.[65,66] Other case studies indicate that aerobic exercise training may increase hippocampal volume and integrity in this population.[26,27] These structural brain observations may explain exercise training effects on ambulation and cognition,[67] but we do not have evidence from Phase II RCTs nor ontological mechanisms for explaining why the structural changes occur with exercise training in MS. This likely represents a key limitation in clinical translation of exercise, as healthcare providers seek firm, mechanistically-derived evidence for making recommendations regarding any approach for treating MS. Without a clear picture of underlying mechanisms resulting in testable theoretical frameworks, clinicians are left wondering why exercise would work for improving outcomes in MS. This might further reflect a problem with translation whereby patients with MS might seek a mechanistic explanation or rationale for exercise benefits. Clearly, stronger research in this area is needed to provide more convincing evidence for possible mechanisms of exercise effects on the CNS in MS (i.e., Is exercise a countermeasure for CNS decline in MS?).

Conceptual Framework and Toolkit for Translating the Evidence

The development of a strong knowledge base supported by mechanisms with substantial scope for application across MS phenotypes (i.e., limitations 1 and 2) is a first step in exercise adoption and adherence among people with MS. We further need a detailed understanding of the potential within the patient-provider interaction (i.e., conceptual framework) and an associated toolkit for translating knowledge on exercise into practice through providers. This would require a focus on the healthcare provider as an external agent for translation of knowledge about exercise and its promotion through clinical care of MS patients. For example, the patient-provider interaction might represent an opportunity for inclusion of advice on benefits as well as counseling on barriers and facilitators into the promotion and prescription of exercise in MS (e.g., clinicians may target self-efficacy via social persuasion for promoting exercise behavior change in a patient for management of fatigue).

The translation of evidence into practice (e.g., comprehensive care of MS by healthcare providers) might be a key factor undermining the adoption and maintenance of exercise behaviors in persons with MS. That is, research indicates that people with MS seek information on behavioral approaches for managing MS and optimizing wellness, particularly exercise and diet.[68] One initial survey-based study of 930 Americans with MS indicated that 34-50% of people, depending upon the healthcare setting, wanted substantially more information about exercise and nutrition in the context of healthcare services.[69] Based on this early work, more recent qualitative research has indicated that people with MS want the promotion of exercise behavior through interactions with healthcare providers.[70,71] The group of healthcare providers is supportive of exercise promotion as part of comprehensive MS healthcare.[72] Collectively, the healthcare setting and associated providers, including neurologists, (neuro)psychologists, nurses, and occupational and physical therapists, are strategically positioned for addressing issues surrounding exercise adoption and adherence in MS,[38] and yet providers may not have the knowledge base, models, tools, or resources for capitalizing on this opportunity. The notion of focusing on the provider for promoting exercise is not necessarily new,[73] but represents a fresh perspective in MS that is particularly suited for this population considering the importance placed on ongoing, comprehensive care through the patient-provider interaction.

Of note, there is quantitative and qualitative evidence that people with MS seek and want support for exercise promotion by providers within the context of comprehensive care,[70] particularly through face-to-face interactions.[71] Qualitative data from two papers of the same sample of persons with MS (*N*=50) in the USA[70,71] indicated a need for (a) information on the benefits of exercise and its prescription, (b) materials supporting home and community exercise, and (c) tools for initiating and maintaining exercise behavior through interactions with healthcare providers across levels of disability and physical activity. Providers too are interested in, and capable of, addressing the unmet needs of people with MS for exercise promotion.[72] Qualitative data from Neurologists, Occupational Therapists, Physical Therapists and Nurses (*N*=44) in the USA indicated that providers identify opportunities for exercise promotion through the healthcare system and comprehensive team during clinical appointments.[72] Providers particularly seek professional and service training for information on benefits of exercise, provision of protocols for exercise promotion, and prescriptive exercise guidelines for promoting behavior change among people with MS.[72]

The aforementioned research is consistent with a participatory action framework of involving patients and providers into the process of forming an action plan for promoting exercise through the patient-provider interaction.[74,75] Such information must now be organized into a framework through concept mapping (i.e., diagram that represents relationships among ideas) that will yield a toolkit supporting knowledge translation consistent with implementation science (i.e., study of methods for uptake of research findings into routine healthcare in clinical contexts). This is of considerable importance given that emphasis on the putative benefits of exercise in persons with MS is a relatively recent phenomenon, as clinicians have been prescribing rest for improving function and symptoms in this population for decades.[76] Indeed, despite relatively weak evidence, energy conservation techniques for reducing fatigue are still commonly practiced in MS rehabilitation settings.[77] Perhaps the dogmatic shift from 'exercise is fatiguing' toward 'exercise reduces fatigue' is slowly being adapted, given the recent surge of evidence supporting the benefits of exercise in this population.[18-20] Such a shift in clinical practice mirrors that which is currently occurring in persons with stroke.[78] This underscores the need for carefully completed evidence-based practice guidelines supporting the beneficial effects of exercise in MS for the development of toolkits for improving exercise promotion by healthcare providers.

Moving Toward Knowledge Translation into Clinical Practice

The notion of knowledge translation involves moving research findings into practice, and there are five main themes around knowledge translation:[79] 1. What should be transferred? 2. To whom should research knowledge be transferred? 3. By whom should research knowledge be transferred? 4. How should research knowledge be transferred? 5. With what effect should research knowledge be transferred?. We believe that addressing the three key limitations in research on exercise training in MS will advance our knowledge regarding four of the five themes involving knowledge translation. For example, tackling the first and second limitations will be necessary for addressing the question of "what research knowledge should be transferred?", whereas targeting the first limitation will be required for answering "to whom should research knowledge be transferred?". Focusing on the third limitation will provide direction on "How" and "By whom" research knowledge should be transferred. Those three limitations are interlaced, and could be addressed through the formation of an international collaborative research network that improves the translational research pipeline for moving knowledge into practice, as undertaken in stroke.[80] The development of collaborative opportunities with implementation scientists will be essential for addressing the fifth theme involving an approach and process for evaluating the effect of knowledge translation as it relates to exercise and MS. Collectively, the limitations we identified have direct relevance for knowledge translation on exercise promotion in persons with MS. This multifaceted approach will be critical for facilitating and supporting the integration of research on the beneficial effects of exercise into the clinical practice of those providing care to persons with MS (i.e., implementation science). Importantly, these 5 main themes are critical for delineating a better roadmap for future research.

Conclusions and Future Directions

Exercise is one of the best rehabilitation approaches for managing symptoms, restoring function, optimizing QOL, promoting wellness, and boosting participation in activities of daily living in MS. Nevertheless, there is a disconnect between the published evidence of benefits from exercise training in persons with MS and the alarming rates of physical inactivity in this population. Although this conundrum is likely multifactorial, the patient-provider interaction is an understudied and especially critical aspect for promoting physical activity participation and increasing the likelihood that persons with MS will realize exercise-related benefits on fitness, symptoms, and function. Addressing gaps between research and practice for improving promotion of exercise via the patient-interaction could, in turn, influence other explanatory factors for the lack of exercise participation in this population (i.e., clinicians helping to improve self-efficacy via social persuasion).

We highlight that future research can improve upon the quality and scope of existing evidence regarding the benefits of exercise training in MS for better informing clinical care of people with MS by addressing the priorities identified in a recent paper on future research in MS.[51] For example, future research efforts must pre-screen participants based on having the consequence that is the primary study outcome (i.e., targeting severely fatigued persons with MS for an exercise intervention for reducing fatigue). This is critical considering that such disease-related consequences are common and highly burdensome in this population. Such interventions further should be adequately powered and include blinded outcome assessors. Indeed, this may involve designing more specific, targeted exercise interventions in representative MS populations for truly understanding the impact of exercise training on focal outcomes. As there is currently a dearth of evidence regarding the effects of exercise training in persons with progressive MS with severe ambulatory disability, there must be a broadened scope of exercise research that examines possible benefits in this cohort. In addition, future research efforts should delineate how to optimize adherence and compliance within the context of a given intervention, such that persons with MS can maximally realize the potential benefits of exercise training. Collectively, addressing these limitations could improve promotion of exercise via the patient-provider interaction. Stronger research efforts in this area are needed to provide more convincing evidence for possible mechanisms of exercise effects on the CNS in MS; this might strengthen the confidence of healthcare providers for prescribing exercise in MS patients. Nevertheless, we underscore the importance of knowledge translation and implementation science for directly bridging the data arising from exercise research on the one hand and clinical practice in this population on the other. This includes better equipping both providers and people with MS for adopting exercise behavior as an approach for managing the numerous debilitating consequences of MS.

Contributors: RWM was responsible for the conceptual design, literature search, drafting of the manuscript, and critical revision of the manuscript. BMS was responsible for the conceptual design, literature search, and critical revision of the manuscript. GK, UD, AF, CH, PF, and AJT were responsible for the conceptual design and critical revision of the manuscript.

Declaration of interests: RWM received grants from National MS Society, grants and personal fees from EMD Serono, grants from Consortium of MS Centers. AF received speaker's honoraria from Biogen, EMD Serono, Roche, Novartis and has received personal fees from Sanofi-Genzyme. PF received grants from PMSA, personal fees from Neurocompass; and President of RIMS, the European network for MS rehabilitation, best practice and research. AJT received personal fees, travel expenses, and honoraria from MedDay, Novartis, Biogen Idec, and TEVA; and has received personal fees from Eisai Ltd, honorarium from SAGE Publications; Chair, Scientific Advisory Board, International Progressive MS Alliance (PMSA), support for travel Member; National MS Society (USA), Research Programs Advisory Committee, support for travel; Chair, International Medical and Scientific Board, and Board Member (2005-2015) Multiple Sclerosis International Federation (MSIF), support for travel; member, MSIF International Medical and Scientific Board (2015-present); Received honoraria and support for travel for lecturing from EXCEMED and Remedica. All other authors declare no competing interests.

Acknowledgments: RWM reports grants from National MS Society, grants and personal fees from EMD Serono, grants from Consortium of MS Centers. PF reports grants from PMSA.

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Panel 1: Definitions of physical activity, exercise, and fitness.[2]

Physical activity = any bodily movement produced by contraction of skeletal muscles that results in a substantial increase in energy expenditure over resting levels.

Exercise = subset of physical activity that is planned, structured, and repetitive with the objective of improving or maintaining physical fitness.

Physical fitness = set of characteristics or attributes that people have or achieve that describe the capacity for performing physical activity.

Panel 2: Search strategy and selection criteria.

References for this Personal View were identified by searches of PubMed, Google Scholar, Scopus, and CINAHL between January, 2012 and July, 2017, and references from relevant articles. The search terms were ‘multiple sclerosis’, ‘exercise’, ‘physical activity’, ‘physical fitness’, and ‘rehabilitation.’ We focused on meta-analyses, Cochrane reviews, and narrative, systematic reviews in order to capture the broad scope and overall effects of exercise on various consequences of MS, given that separately reviewing over 60 individual clinical trials of exercise in MS would extend beyond the scope of the current paper. We only reviewed papers that were published in English. The final reference list was generated on the basis of relevance to the focus of this Personal View.

Table 1: Effects of exercise training in persons with MS.

Outcome	Study	Design	Primary Purpose	Number of Studies Included	Primary Results/Effect Sizes	Quality Indices	Limitations of Research Body
Physical Fitness	Kjølhede et al., 2012[4]	Systematic Review	Effects of resistance exercise on muscular strength outcomes in MS	16	7-21% improvement in lower limb MVC; 20-50% improvement in lower limb 1-RM *d*-values: NR	Mean PEDro score = 5.0	Small sample sizes (risk of Type II error); lack of blinded assessors
	Langeskov-Christensen et al., 2015[5]	Meta-Analysis	Effects of exercise on aerobic capacity in MS	17	Moderate improvements in VO_{2peak} (d=0.63)	Mean PEDro score = 5.5	Lack of severely disabled samples
	Platta et al., 2016[6]	Meta-Analysis	Effects of exercise training on fitness in MS	20	Improvements in muscular fitness (d=0.27) and cardiorespiratory fitness (d=0.47)	<u>Combined exercise:</u> *Mean PEDro score = 6.6 <u>Aerobic exercise:</u> *Mean PEDro score = 7.2 <u>Resistance exercise:</u> *Mean PEDro score = 6.7	Overall lack of studies reporting fitness measures; low quality outcome measures; lack of severely disabled samples; lack of concealed allocation; lack of blinded participants, assessors, therapists, lack of ITT analyses
Walking Mobility	Pearson et al., 2015[8]	Meta-Analysis	Effects of exercise on mobility in MS	13	Overall clinically meaningful improvements in 10mWT (17%) and 2MW (19%); Overall significant, but non-	*Mean PEDro score = 6.0	Heterogeneous interventions; no dose-response studies; lack of comparisons of exercise

					clinically meaningful improvements in T25FW, 6MW *d*-values: NR		modalities
	Learmonth et al., 2016[9]	Meta-Analysis	Effects of physiotherapy treatment on walking performance in MS	21	Improvements in walking outcomes (*d*=0.25); similar across treatment protocols	*Mean PEDro score = 6.0	Heterogeneous treatment protocols
Balance	Paltamaa et al., 2012[11]	Meta-Analysis	Effects of physiotherapy interventions on balance outcomes in MS	7	Small, but statistically significant beneficial effects on balance (*d*=0.34)	Mean Van Tulder score = 4.4 PEDro score: NR	Small, underpowered studies; lack of blinding; lack of reporting of intervention and randomization protocols
Cognition	Sandroff et al., 2016[14]	Systematic Review	Effects of exercise, physical activity, physical fitness on cognition in MS	26	Conflicting evidence for exercise effects; preliminary evidence supporting beneficial effects of physical activity and physical fitness on cognition *d*-values: NR	<u>Exercise:</u> *Mean PEDro score = 7.0 <u>Physical activity:</u> *Mean PEDro score = 6.0 <u>Physical fitness:</u> Mean PEDro score = N/A	Cognition not included as primary outcome; poorly-developed exercise interventions; lack of cognitively-impaired samples
Fatigue	Pilutti et al., 2013[18]	Meta-Analysis	Effects of exercise training on fatigue in MS	17	Consistent, moderate reductions in fatigue (*d*=0.45)	*Median PEDro score = 6.0	Heterogeneous interventions; lack of progressive MS samples; persons

							not pre-selected for fatigue; lack of blinded assessors; lack of ITT analyses
	Asano et al., 2015[19]	Meta-Analysis	Effects of exercise, education, and pharmacotherapy on fatigue in MS	25 (10 of 25 studies on exercise)	Moderate reductions in fatigue (*d*=0.57), similar to effects of educational interventions (*d*=0.54)	Overall Risks of Bias: Selection bias; lack of concealed allocation; incomplete outcomes reported; selective reporting of outcomes PEDro score: NR	Heterogeneous interventions; lack of pre-screening for fatigued persons; lack of concealed allocation; incomplete outcome reporting; selective reporting of outcomes
	Heine et al., 2015[20]	Cochrane Review	Effects of exercise therapy on fatigue in MS	45	Moderate reductions in fatigue (*d*=0.53)	Mean PEDro score = 5.2	Underpowered studies; lack of recruiting based on having severe fatigue; lack of therapies targeting fatigue
Depressive Symptoms	Ensari et al., 2014[21]	Meta-Analysis	Effects of exercise training on depressive symptoms in MS	13	Small, consistent improvements in depressive symptoms (*d*=0.36)	Mean PEDro score = 5.8	Lack of blinded assessors; lack of primary focus of interventions; lack of pre-screening for depression
	Dalgas et al., 2015[22]	Meta-Analysis	Effects of exercise training on depressive symptoms in MS	12	Small, consistent improvements in depressive symptoms (*d*=0.37)	Mean PEDro score = 5.6	Heterogeneous interventions; depression not primary outcome; no studies on

							MDD; lack of progressive MS samples; lack of control for anti-depressant medications
	Adamson et al., 2015[23]	Meta-Analysis	Effects of exercise training on depressive symptoms in persons with neurological disorders	23 (13 of 23 studies on MS)	Small, consistent improvements in depressive symptoms (*d*=0.28); larger effects when interventions meet physical activity guidelines	Mean PEDro score (MS studies) = 5.5	Lack of studies on MDD; lack of blinded participants, therapists, assessors; lack of AE reporting; inclusion of non-depressed samples
QOL	Latimer-Cheung et al., 2013[24]	Systematic Review	Effects of exercise training on fitness, mobility, fatigue, and health-related QOL in MS	26	Conflicting evidence for effects on QOL *d*-values: NR	<u>Aerobic exercise:</u> *Mean PEDro score = 7.5 <u>Resistance exercise:</u> *Mean PEDro score = 8.5 <u>Combined exercise:</u> *Mean PEDro score = 7.7 <u>Other exercise:</u> *Mean PEDro score = 7.0	Overall lack of reporting on safety of exercise training; heterogeneous interventions; equal monitoring of persons in exercise and control conditions

Note: *PEDro scores ≥ 6.0 are indicative of good methodological study quality; 1-RM=1-repetition maximum; 2MW=Two-minute walk; 6MW=Six-minute walk; 10mWT=Ten meter walk test; AE=Adverse event; ES=Effect size; ITT=Intent-to-treat; MDD=Major depressive disorder; MS=Multiple sclerosis; MVC=Maximal voluntary contraction; NR = not reported; PEDro=Physiotherapy Evidence Database; QOL=Quality of life; SMD=Standardized mean difference; T25FW=Timed 25-foot walk; VO_{2peak}=Peak oxygen consumption; Effect sizes interpreted as small, moderate, and large based on Cohen's *d*-values of 0.2, 0.5, and 0.8, respectively.