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Benefits of Exercise Training in Multiple Sclerosis

Robert W. Motl[1] · **Brian M. Sandroff**[1]

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Abstract Exercise training represents a behavioral approach for safely managing many of the functional, symptomatic, and quality of life consequences of multiple sclerosis (MS). This topical review paper summarizes evidence from literature reviews and meta-analyses, supplemented by recent individual studies, indicating that exercise training can yield small but important improvements in walking, balance, cognition, fatigue, depression, and quality of life in MS. The paper highlights limitations of research on exercise training and its consequences and future research directions and provides an overview for promotion of exercise training in MS based on recent prescriptive guidelines. Collectively, the evidence for the benefits of exercise training in MS suggests that the time is ripe for the promotion of exercise by healthcare providers, particularly neurologists as a central part of the clinical care and management of MS patients.

Keywords Multiple sclerosis · Exercise · Function · Symptoms · Quality of life

Introduction

Multiple sclerosis (MS) is a prevalent, non-traumatic neurological disease that occurs most often among young and middle-aged women of northern European origin. This disease typically begins with intermittent and recurrent events of multi-focal inflammation in the central nervous system (CNS) that can result in demyelination and transection of axons [1–3]. There are additional neurodegenerative processes that result in neuroaxonal loss throughout the disease course, but these are particularly involved during the later stages of the disease [1–3]. The damage within the CNS accumulates over time (i.e., progression of disease burden) and results in neurological disability, dysfunction of mobility (i.e., walking and balance) and cognition, and symptoms of fatigue and depression [3, 4]. MS and its manifestations can further compromise quality of life (QOL) [5, 6].

Disease-modifying therapies (DMTs) represent the first line of treatment for targeting the immunopathophysiological processes involved in MS [7]. In patients with relapsing MS, DMTs (e.g., Interferons) can decrease the number of lesions based on magnetic resonance imaging (MRI) and the rates of relapse and disability progression [8] but are only modestly effective in slowing progression of neurological disability in the absence of relapses [9, 10]. The DMTs further do not target the multifaceted causes of mobility and cognitive dysfunction, symptoms of fatigue and depression, and compromised QOL in MS [4, 11]. This highlights the importance of identifying other approaches for managing those consequences that can persist over the course of this incurable, disabling disease [12].

Exercise training represents a behavioral approach for safely managing many of the functional, symptomatic, and QOL consequences of MS. Some researchers have argued that exercise training, defined as planned, structured, and repetitive physical activity undertaken for improving one's physical fitness levels [13], is the single most effective non-pharmacological approach for managing symptoms of MS [14] and its functional consequences [12, 15]. Others have argued against such a statement based on an insufficient amount and poor quality of research [16, 17]. Researchers

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✉ Robert W. Motl
robmotl@illinois.edu

[1] Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, 233 Freer Hall, Urbana, IL 61801, USA

have recently reported on the overall safety profile of exercise training in MS, including a reduced rate of reported relapses (i.e., approximately 27 % lower relapse rate for exercise training conditions versus non-exercise control conditions) and minimal, exercise-related adverse or serious adverse events in randomized controlled trials (RCTs) [18]. There is even some speculation that exercise training might exert a disease-modifying effect in MS [19], although the evidence is minimal and speculative, particularly when considering the effect of exercise training as a disease-modifying behavior in preclinical research using animal models of MS [20]. Regardless, exercise training as a form of rehabilitation is of major importance in minimizing the influence of this disease on the lives of people with MS [12].

The current paper provides a topical review on the benefits of exercise training that can inform healthcare providers, particularly neurologists, in the comprehensive care of MS patients. This is important considering that patients want advice on exercise training from healthcare providers [21], yet providers often do not have adequate resources for meeting this need (e.g., encouraging, promoting, and prescribing this behavior among patients) [22]. To that end, this paper focuses on the benefits of exercise training for improving mobility and cognitive outcomes, symptoms of fatigue and depression, and QOL based on the prevalence and burden in MS patients. The paper primarily describes (a) evidence for the benefits of exercise training that has been summarized in literature reviews and meta-analyses and (b) exemplar RCTs when the evidence from reviews is equivocal and inconclusive, but recent evidence is intriguing and supportive, yet preliminary. The paper further highlights limitations of research on exercise training and its consequences and future research directions and provides an overview for promotion of exercise training in MS based on recent prescriptive guidelines [23].

Benefits of Exercise Training in MS

There have been over 50 clinical trials examining the benefits of exercise training in persons with MS [23]. The number and range of studies combined with heterogeneity of primary and secondary outcomes makes a comprehensive review of this research body insurmountable. The volume and breadth further negates the possibility of focusing only on individual studies for discussion in this review paper, other than presenting selective exemplars that provide exciting and recent evidence for benefits of exercise training. To that end, there have been many literature reviews and meta-analyses that allow for a focal description of the benefits of exercise training in persons with MS who are ambulatory (i.e., mild or moderate MS disability). Conversely, there is insufficient evidence for a clear case regarding the benefits of exercise training in non-ambulatory people with MS. This section will summarize the evidence regarding exercise training and walking [24, 25], balance [26], cognition [27, 28], symptoms of fatigue [29, 30] and depression [31–33], and QOL [23, 34]. The focus on fitness outcomes, whereas important, is beyond the scope of this review and not of central relevance in the clinical care and management of MS and its consequences per se.

Walking Mobility The loss of walking mobility is a hallmark feature of MS and its progression [35]. The loss of walking further is one of the most burdensome and troubling features of MS [36], and patients with MS place considerable value on this particular function [37]. There is evidence for improvements in walking outcomes with exercise training in MS [24, 25], and this might occur through effects on either the CNS (e.g., integrity of cortical or subcortical grey matter structures such as thalamus or basal ganglia) [38] and/or peripheral physiological functions (e.g., cardiorespiratory capacity or muscle strength/endurance) [39].

Researchers have undertaken meta-analyses [24, 25] examining the effect of exercise training on walking outcomes in persons with MS. The first meta-analysis [25] searched multiple electronic databases for articles published between 1960 and November 2006 using key concepts for exercise and mobility along with MS, and this was supplemented by manual searches of references from retrieved articles and literature reviews. The search included RCTs and non-RCTs and yielded 22 total papers containing 600 persons with MS. The weighted mean effect size (ES) was 0.19 units (this is in standard deviation, SD, units), and there was minimal evidence for heterogeneity of the average effect size. The exploratory moderator analyses suggested that supervised exercise training (weighted mean ES=.32) was more effective for improving walking outcomes than non-supervised training (weighted mean ES=.03).

Another meta-analysis [24] searched electronic databases for articles published between 1966 and March 2014 using key concepts of “exercise” and “multiple sclerosis.” The researchers further performed manual searches of references from retrieved publications and only included RCTs with a post-intervention sample size exceeding 10 subjects. The search yielded a total of 13 papers that included 655 people with MS (357 engaged in exercise training and 298 were in control conditions). The median Physiotherapy Evidence Database (PEDro) score for the 13 RCTs was 6.0, with all studies scoring 5 or more, indicating a generally strong body of research. The meta-analysis yielded clinically meaningful improvements in 10-m walk time (10 mWT) (16.5 % improvement) and 2-min walk (2 MW) distance (19 % improvement), as well as non-clinically meaningful improvements in T25FW performance (0.6 s improvement), 6 MW distance (34.5 m improvement), and timed-up-and-go (TUG) time (1.1 s improvement).

Collectively, there is a consistent and small, but important benefit of exercise training on walking mobility in MS. The

effect is larger with supervised exercise training that seemingly maximizes compliance with the exercise program and prescription. Of note, there was limited evidence for long-term maintenance effects of exercise training on walking outcomes. Other notable limitations included a lack of comparing exercise training effects on walking across clinical courses of MS (e.g., relapsing-remitting vs. primary progressive MS) or benchmarks of disability status that indicate accrual of mobility impairment (e.g., <4.0 vs. 4.0–6.0 on Expanded Disability Status Scale).

Balance Abnormalities of balance (i.e., the maintenance of upright posture) represent another domain of mobility that is compromised in MS. The effect of MS on balance is typically quantified based on increased sway during quiet stance [40]. Importantly, balance problems may be associated with falls and fall-related injuries [41], and measures of postural sway have been associated with walking [39] and cognitive performance in MS [42]. Abnormalities of balance might further restrict community participation in persons with MS [43].

One group of researchers conducted a systematic review and meta-analysis of RCTs published up through March of 2011 involving exercise training for improving balance in MS [26]. The search resulted in 233 full-text articles that were assessed for eligibility, and 11 studies were included in the qualitative synthesis, but only 7 papers met the inclusion criteria and provided enough data to compute ESs for the meta-analysis. Overall, there was a small, but statistically significant effect of the exercise training modalities on balance in persons with mild or moderate MS.

We are aware of one recent exemplar study that examined the effect of home-based balance training using the Nintendo Wii balance board system (WBBS) on postural control, mobility, and microarchitecture changes in brain white matter tracts in 36 persons with MS who had an objective balance disorder [40, 44]. The researchers adopted a two-period crossover design wherein one group received 12 weeks of home-based WBBS training followed by a 12-week period without intervention (group A), whereas the other group received treatments in the reverse order (group B). The primary endpoints included displacement of body center of pressure (COP) on a force platform, T25FW, four-step square test (FSST), and diffusion-tensor imaging of cerebellar connections. The WBBS training occurred for 30 min per day on a daily basis over a 12-week period; the research permitted skipping a maximum of one session per week. Participants played a set of three standard WBBS core games during the first 4 weeks of the intervention, followed by inclusion of additional games over the residual of the intervention period. There were significant improvements in COP, FSST, and T25FW in group A after the 12-week period of WBBS training, and these were not maintained during the observational follow-up period; the opposite pattern of changes occurred in group B [40]. There were further significant changes in fractional anisotrophy and radial diffusivity of the left and right superior cerebellar peduncles that correlated with changes in COP metrics from the force platform; those with reduced postural sway demonstrated better white and grey matter integrity in cerebellar regions involved in balance [44].

Overall, there is a small benefit of exercise training on balance in MS, and this improvement might be explained by microstructural changes in brain regions associated with postural control and balance. The methodological quality of many studies, however, ranged from poor through moderate, and the sample sizes were typically small (i.e., 4–40 per treatment group) [26]. This limits the internal validity of those studies and renders strong conclusions regarding exercise training and balance in MS premature, although recent evidence has provided important insights on possible mechanisms for improvement in balance with exercise training [40, 44].

Cognition Cognitive dysfunction is a prevalent and burdensome consequence of MS [45] and primarily manifests in domains of information processing speed, learning and memory, and executive function [46]. Cognitive dysfunction has been associated with unemployment and loss of employment, as well as reduced social functioning and loss of driving abilities in persons with MS [45].

There is a corpus of evidence indicating that exercise training influences cognitive function in older adults, children, and adolescents [47, 48], and even persons with schizophrenia [49]. By comparison, one literature review reported inconsistent evidence from research examining the effects of exercise training on cognition in MS [28], and this was confirmed in a separate systematic review of exercise training and cognitive function in adults with neurological diseases, including MS [27]. That review included seven clinical trials with 249 participants and noted that there was limited evidence that supports aerobic exercise training for improving cognition in adults with neurological disorders [27].

Of note, two recent trials demonstrated improvements in some domains of cognition after exercise training in MS [50, 51] and one paper reported improvements with a lifestyle, physical activity program focusing on walking [52]. One study compared three aerobic exercise training conditions with a waitlist control condition for improving attention, cognitive processing speed, long-term memory, and executive function in a pilot RCT of persons with secondary progressive MS [50]. The sample included 42 MS patients with a secondary progressive clinical disease course (EDSS=4.0–6.0) who were randomly assigned into one of four conditions; supervised cycle ergometry, arm ergometry, or rowing, and waitlist control. The exercise training took place two to three times per week over 8–10 weeks. The duration steadily increased across the program, for all exercise conditions, from 15–45 min per session, at an intensity between 120 and 130 % of anaerobic

threshold. All three exercise training conditions improved verbal learning and delayed recall on the Verbal Learning and Memory Test (VLMT), whereas there were selective changes in alertness for primarily cycle ergometry. There were no effects on cognition for the control condition. There were further no intervention effects for cognitive processing speed based on Symbol Digit Modalities Test scores, executive function, or verbal fluency. There were significant associations between changes in aerobic capacity (i.e., VO_{2peak}) and VLMT performance. This suggests that increasing aerobic capacity might be a potential mechanism for improvements in verbal memory with aerobic exercise training in persons with progressive MS.

We are aware of one intriguing case study that collected data from two ambulatory, memory-impaired persons with MS who were assigned into non-aerobic (i.e., stretching or active control; MS duration=15 months, age=33 years) and aerobic (stationary cycling; MS duration=15 months, age=44 years) exercise training conditions [51]. The two conditions involved exercising 30-min per session three times per week over a 12-week period. Aerobic exercise training resulted in a 16.5 % increase in hippocampal volume, 55.9 % increase in verbal memory, and 53.7 % increase in non-verbal memory, as well as increased hippocampal resting-state functional connectivity. The non-aerobic exercise condition demonstrated minimal change in hippocampal volume (2.8 %), no changes in verbal or non-verbal memory (0.0 %), and no change in hippocampal resting-state functional connectivity. This suggests that aerobic exercise training could improve domains of cognitive performance through neuroplasticity in MS.

Overall, the research on exercise training and cognition in MS, and other neurological conditions, is in a stage of infancy and does not permit strong or clear conclusions because of methodological limitations. One limitation may be that few studies continued aerobic exercise programs long enough for effectiveness in changing cognition (e.g., 3–6 months) [27]. Another limitation may be poor compliance with the exercise program and prescription, as the exercise training was largely home-based without sufficient supervision or monitoring [28]. This underscores the importance of additional, well-designed studies of exercise training on cognition in neurological conditions, particularly MS.

Fatigue Fatigue is one of the most common and burdensome symptoms of MS. Fatigue occurs in nearly 80 % of people with MS [53] and has major implications for worsening of neurological disability and other symptoms such as depression, pain, anxiety, and cognitive impairment (i.e., symptomatic clustering) [54]. Fatigue further can contribute toward cessation of employment in MS [53]. There is evidence that exercise can assist in managing energy and fatigue levels in the general population [55], but there has been previous concern that exercise might worsen fatigue in MS by taxing energy levels and reserves [53] or increasing core body temperature.

Researchers have undertaken meta-analyses [29, 30] examining the effect of exercise on symptomatic fatigue in persons with MS. The first meta-analysis [30] broadly searched electronic databases for articles published between 1960 and October 2012 using key concepts for fatigue and exercise, and the researchers performed manual searches of references from retrieved articles and other literature reviews. The search resulted in 311 articles, and 17 papers both met the inclusion criteria and provided enough data to compute ESs. The weighted mean ES from the 17 RCTs containing 568 persons with MS was 0.45 units (this is in SD units), but there was minimal evidence for heterogeneity of the average ES.

The other meta-analysis examined multiple types of interventions, including exercise training, education self-management, and medication, for fatigue in MS [29]. The researchers extensively searched databases through August of 2013 using key concepts of fatigue and energy conservation. The search identified 230 citations, and after full-text review yielded 18 rehabilitation (exercise or education self-management) and 7 pharmacological trials. Rehabilitation interventions were more effective than pharmacological interventions (7 studies of 604 people with a mean ES of 0.07), and exercise training (10 studies of 233 people with MS) yielded a mean ES of 0.57 units compared with the mean ES of 0.54 units for educational self-management trials (eight studies of 662 people with MS).

Collectively, exercise training resulted in a ~1/2 SD reduction in fatigue compared with control conditions, and there was little variability across study and sample characteristics. Such results would support that exercise training exerts a clinically meaningful improvement [56] in fatigue among those with MS, and exercise training is as effective as educational self-management for reducing fatigue in MS. One caveat of the research on exercise training is that samples often have not been pre-selected or recruited for severe or impactful symptoms of fatigue, and this limits the generalizability amongst those with such manifestations.

Depressive Symptoms Depression and depressive symptoms are quite common and burdensome symptoms that occur with MS. For example, one study using the UK MS registry included data from 4178 persons with MS and reported that persons with MS had a mean Hospital Anxiety and Depression Scale (HADS) depression score of 7.6 compared with the reference value of 3.7 for UK population; HADS scores greater than 7 are indicative of substantial depressive symptoms [57]. Depression and depressive symptoms have major implications for cognitive impairment, QOL, and compliance with disease-modifying agents in MS [58]. The American Academy of Neurology reported that there was insufficient evidence for the efficacy of antidepressant medications or therapies for managing depression in MS [59]. By comparison, there is a

substantial body of research supporting the antidepressant effects of exercise training in the general population of adults [60], but reviews of similar evidence in MS have been equivocal [61]. Such observations prompted meta-analyses quantifying the overall effect of exercise training on depressive symptoms in MS [31, 32] and neurological disorders, including MS [33].

One of the meta-analyses broadly searched electronic databases for RCTs of exercise training and MS over the period of 1960 through November 2013 [32]. The researchers further performed manual searches of references from retrieved articles and other literature reviews. The search yielded 25 papers on depression and exercise in MS, and there were 13 RCTs that met inclusion criteria and yielded data for ES generation. The weighted mean ES was 0.36 units, and there was minimal evidence for heterogeneity. Those results were confirmed in another meta-analysis of essentially the same RCTs, wherein the researchers reported an ES of 0.37 SD units [31].

Another paper has recently been published describing a systematic review and meta-analysis of exercise training effects on depression and depressive symptoms in neurological populations [33]. The researchers extensively searched electronic databases for articles published through May 2014 using acronyms for neurological conditions (e.g., nervous system diseases) and physical activity (e.g., exercise). The search resulted in 43 full-length articles that were evaluated in detail and 26 papers that met the inclusion criteria; 3 studies were excluded from the meta-analysis as there was insufficient data for computing ESs. The weighted mean ES from the 23 RCTs containing 1324 subjects was 0.28 units (this is in SD units), and there was modest evidence for heterogeneity of the average ES. The only significant moderator was physical activity guidelines (PAGs); the effect of exercise training on depressive symptoms was significantly larger in those interventions meeting PAGs (e.g., 150 min per week of moderate intensity exercise or 75 min per week of vigorous intensity exercise) (.49 SD unit improvement) compared with those not meeting PAGs (.20 SD unit improvement).

Overall, the two meta-analyses in only those with MS indicated that exercise resulted in a ~1/3 SD improvement in depressive symptoms compared with control conditions, and this effect was not explained by study and sample characteristics. Another meta-analysis indicated that exercise training resulted in a ~1/2 SD reduction in depressive symptoms among persons with neurological conditions including MS, when participants engaged in sufficient amounts of exercise training that satisfied PAGs. Such results would suggest that exercise is generally beneficial for managing symptoms of depression in MS. This research has not included major depressive disorder as a primary inclusion criterion or outcome, thereby limiting the conclusions regarding exercise training beyond depressive symptomology in MS.

Quality of Life Persons with MS have lower health-related and overall QOL (HRQOL) than non-diseased populations [5, 6] and those suffering from other serious diseases including inflammatory bowel disease, ischemic stroke, and rheumatoid arthritis [62–64]. This might be associated with the uncertain and unpredictable nature of a currently incurable disease with onset during the most productive years of one's life [5, 6]. The effect of MS on QOL might further be associated with the worsening of symptoms and dysfunction of walking and cognition in MS [5, 6]. This underscores the importance of identifying methods of managing this downstream and often inevitable consequence of MS.

One older meta-analysis quantified the overall effect of exercise on QOL among those with MS [34]. The researchers searched databases for the period of 1960 to November 2006 using key concepts for exercise training in conjunction with QOL and MS. The researchers further conducted a manual search of bibliographies of papers and contacted study authors about other publications. Twenty-five journal articles were located and reviewed, and 13 provided enough data to compute ESs; there were 109 ESs from 484 persons with MS. The overall weighted mean ES was 0.23 units. The mean ES was heterogeneous, and the effect was largest with MS-specific QOL measures and aerobic exercise training. Collectively, the cumulative evidence supported that exercise, particularly of an aerobic or cardiorespiratory nature, was associated with a small, ~1/4 SD improvement in QOL.

We are aware of one recent systematic review of exercise training wherein the paper included a focus on HRQOL in adults with MS [23]. The review was limited to English language studies (published before December 2011) of people with MS that evaluated the effects of exercise training on outcomes of physical fitness, mobility, fatigue, and/or HRQOL. The search identified 4362 possible studies, and 54 studies were included in the review. Twenty-one of the studies met the systematic review criteria and included at least one measure that evaluated the impact of various forms of exercise training on HRQOL.

Overall, the researchers reported that the current evidence was insufficient for conclusions regarding the effects of exercise training on HRQOL outcomes in persons with MS. Such a conclusion was, in part, associated with methodological limitations including variation in generic vs. disease specific outcomes, reporting of composite vs. domain scores, and focusing on all rather than specific, pre-selected domains of HRQOL.

Summary There is evidence that exercise training is associated with small, but important improvements in walking, symptoms of fatigue and depression, and QOL in persons with MS. Exercise training further has a small and potentially important effect on balance, and recent evidence points toward positive effects on some cognitive functions. This supports the relevance of exercise training for managing some of the

prominent and burdensome consequences of MS, and there is some evidence of more extensive benefits, including effects on disease pathophysiology and brain structure and function based on MRI in persons with MS [65].

Major Limitations

There are major limitations of the existing body of research on exercise training in MS that should be (a) recognized for contextualizing the evidence and (b) overcome in future research. One limitation is that the samples often include persons with mild, sometimes moderate, neurological disability and a relapsing-remitting course of MS. We know very little about exercise training benefits in persons with severe neurological disability (i.e., non-ambulatory persons with MS) or progressive clinical courses of MS (i.e., primary or secondary progressive MS). The majority of research does not recruit and enroll samples with a known condition (e.g., cognitive or walking dysfunction) or symptom (e.g., severe fatigue or major depressive disorder) when examining the consequences of exercise training in MS. This is a limitation considering that the effects of exercise training for managing a specific condition or elevated symptom associated with MS are largely unknown. Other limitations include poor reporting of research design features (e.g., blinding of assessors and concealed allocation and other features of CONSORT statement), sample descriptive characteristics (e.g., EDSS scores), power analyses, and statistical analyses and results (e.g., mean scores and standard deviations for meta-analyses). This results in an appraisal of low study quality regarding exercise training and its consequences in MS [17] and constrains conclusions to be drawn from existing research. We further do not have RCTs that have delineated the "characteristics" of an exercise program that would optimize the beneficial consequences.

Future Directions

There are many areas of future research that will expand our understanding of exercise training and its benefits in MS. Such future directions have largely been summarized in a paper of top 10 research questions regarding physical activity and MS [66]; 5 of the 10 questions involve consequences of exercise training in MS. There is a need for preclinical research examining the effect of exercise in animal models of MS [20]. Such research is critical for understanding the possible influence of exercise training on the disease pathophysiology of MS. There further is a critical line of research necessary for examining the effects of exercise training on disease pathophysiology in humans with MS (e.g., RCTs that focus on immune cells and neurotrophic factors as well as metrics of brain structure and function from MRI) [65]. Such lines of inquiry will strengthen our understanding of exercise training and its influence as a possible disease-modifying behavior in MS. There is a need for research on exercise alone and combined with DMTs and other symptomatic therapies and approaches for self-management. This will be important for identifying independent and interactive (i.e., additive or synergistic) influences of exercise training in MS. This further is important considering that one approach alone is unlikely to be sufficient in managing the consequences of MS, as a single approach is rarely recommended by healthcare providers for managing MS. We know little about the mechanisms for the benefits of exercise in MS and how the mechanisms might vary by outcomes, stages of the disease, and clinical courses of the disease. We know little about the effects of different modes of exercise training (e.g., aerobic vs. resistance; continuous vs. interval) on consequences of MS, and this has been the focus of recent debate [14, 16]. We need considerable effort directed toward understanding and maximizing compliance with participation in exercise training among persons with MS. This will be essential for motivating long-term behavior change and optimizing the benefits of exercise training over the course of MS, considering that this is a lifelong disease with no known cure [12, 22]. There has been an increasing interest in the study of comorbid conditions in MS, and such conditions have been associated with worsening disease status [67]. There is evidence that exercise training is promising for managing comorbid conditions in the general population, and researchers might further consider the effect of exercise training on comorbid conditions such as cardiovascular [68] and metabolic [69] diseases in MS.

Prescription of Exercise Training for Clinical Care of MS

There is evidence for benefits of exercise training in persons with MS, and this is complemented by recent evidence for its safety. Such evidence has motivated interest in approaches for promoting exercise training in MS patients through healthcare providers and subsequently the development of prescriptive guidelines. To that end, one group recently applied the international standards for guideline development and created evidence-based exercise guidelines for people with MS [70]. The evidence for the guidelines was based on a systematic review of exercise training effects on health-related fitness, fatigue, mobility, and HRQOL among those with MS [23]. The research group for this project consisted of a multidisciplinary consensus panel that deliberated about the scientific evidence and then generated the guidelines and a preamble. The guidelines and materials were then refined after a review by stakeholders and experts. The resulting guidelines indicated adults with MS who have mild or moderate disability should undertake 30 or more minutes of moderate intensity aerobic activity two times per week and strength training exercises for major muscle groups two times per week [70]. If a person meets or exceeds those guidelines, there should be improvements in fitness, symptoms, mobility, and HRQOL.

This represents a starting point for promoting exercise training among patients with MS by healthcare professionals, although these guidelines require verification for improving and possibly maximizing beneficial outcomes.

Conclusion

This paper summarizes evidence from literature reviews and meta-analyses, supplemented by recent individual studies, and the evidence indicates that exercise training can yield small, but important improvements in walking, balance, cognition, fatigue, depression, and QOL. The benefits can be obtained with minimal risk of relapse and other adverse or serious adverse events and likely by following recent prescriptive guidelines for exercise training in MS. Those guidelines are applicable for adults with MS who have mild or moderate disability. The promotion of exercise is ripe for becoming a central part of the clinical care and management of MS patients by healthcare providers.

Compliance with Ethics Guidelines

Conflict of Interest Robert W. Motl reports personal fees from EMD Serono, grants from Acorda Therapeutics, and grants from Biogen IDEC. Brian M. Sandroff declares no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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provides a list of the top 10 research questions for guiding future research on physical activity in multiple sclerosis.

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