# Effect of Comorbidities on Outcomes of Neurorehabilitation Interventions in Multiple Sclerosis

## A Scoping Review

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**Background:** ***Interest in comorbidities has increased in the past few years, but the effect of comorbidities on outcomes of multiple sclerosis (MS) neurorehabilitation interventions is unclear. The aim of this review was to identify and summarize the existing evidence regarding the effect of comorbidities on outcomes of neurorehabilitation interventions targeting people with MS.***

**Methods:** ***Five databases (Embase, MEDLINE through Ovid, PubMed Central, Cumulative Index to Nursing and Allied Health Literature, and Web of Science) were searched using index terms and keywords relating to MS and a wide range of rehabilitation interventions. Studies screened were limited to English-language randomized controlled trials. Information related to included and excluded comorbidities and how they were reported and described was extracted from the included studies.***

**Results:** ***Fifty-four neurorehabilitation randomized controlled trials were included and were grouped into categories: robotics/technology-enhanced (n = 7), task-oriented training/neurorehabilitation principles (n = 7), electrical stimulation (n = 12), temperature regulation (n = 6), magnetic field therapy (n = 5), vibration (n = 9), and miscellaneous (n = 8). Although the issue of comorbidity was considered in 40 studies, it was limited to excluding individuals from participating in the trials. Only two studies reported on comorbidity, but neither examined the possible mediating or moderating effect of comorbidities on intervention outcomes.***

**Conclusions:** ***This review documents important knowledge gaps about the effect of comorbidity on neurorehabilitation outcomes and identifies a critical need for future studies to address this issue. Without this information, we limit our understanding of the mechanisms of comorbidity and its effects on relevant clinical and research outcomes specific to neurorehabilitation.*** ***Int J MS Care.*** **2016;18:282–290.**

Approximately 50% of people with multiple sclerosis (MS) may become moderately to severely disabled within 15 years of disease diagnosis[1]; this proportion increases to 75% after 45 years.[2] An increasing level of disability has substantial consequences for the ability of people with MS to engage in daily activities and maintain social relationships.[3] When MS occurs in the presence of comorbidities, the combined effect of and interactions between conditions often result in a more rapid progression of disability, a reduction in quality of life, and an increase in mortality.[4]

Comorbidity, which refers broadly to physical or mental conditions that exist at the time of diagnosis of MS or later but that are not a consequence of MS, occurs in up to 50% of individuals with this disease.[5]

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Note: Supplementary material for this article is available on IJMSC Online at ijmsc.org.

DOI: 10.7224/1537-2073.2016-015

The most common physical comorbidities in people with MS include hypertension, hyperlipidemia, and chronic lung disease. Mental conditions, such as depression and anxiety, are also commonly reported.[6]

Despite advances in disease-modifying therapies that may reduce disease progression, the residual level of disability remains unchanged.[7] Consequently, neurorehabilitation interventions are needed to manage the consequences of MS.[8] For the purposes of this study, we defined neurorehabilitation interventions as any treatment activities or services aimed at reducing the effect of disability resulting from MS using the principles of neuroplasticity.[9]

Researchers have shown that neurorehabilitation interventions can improve physical function, increase activity and participation, and optimize the quality of life of people with MS.[10] Given the high prevalence of comorbidities in MS and the desire of clinicians to apply evidence-based practices, it is critical to understand the extent to which neurorehabilitation researchers have considered the presence of comorbidities in the course of their studies. This knowledge would guide the application of evidence in real-life settings.

Scoping reviews provide a synthesis of research on a particular topic by describing emerging trends and identifying gaps in knowledge.[11] Given the breadth of rehabilitation interventions targeting people with MS, we conducted this scoping review as part of an ongoing study aimed at documenting the effect of comorbidities on rehabilitation intervention outcomes. In particular, this review focuses on identifying gaps and summarizing existing evidence regarding the effect of comorbidities on neurorehabilitation outcomes. Two research questions guided this review: 1) Do neurorehabilitation interventions targeting people with MS address participant comorbidities? If so, how? 2) What are the gaps in current knowledge about the effect of comorbidities on neurorehabilitation intervention outcomes?

## Methods

We used the framework put forth by Arksey and O'Malley.[11]

### Search Strategy

Five databases were searched to locate articles published from inception to January 8, 2016 (Embase, MEDLINE through Ovid, PubMed Central, Cumulative Index to Nursing and Allied Health Literature, and Web of Science). First, we searched *multiple sclerosis* as an index term and a keyword, and then we combined the results using the operator *OR* in each database. Next, we added database-specific terms for randomized controlled trials (RCTs) to limit the results to intervention research. We focused on RCTs because they are the gold standard for evaluating intervention efficacy and effectiveness.

Next, we conducted a series of searches using database-specific index terms (eg, Medical Subject Headings) that captured the focus or content of a wide range of rehabilitation interventions. These terms included *rehabilitation, exercise, physical activity, motor activity, fitness, self-care, self-management, health promotion, health education, patient education, health behavior, assistive technology, assistive device, self-help, behavior modification, environment, home environment,* and *modification*. Each term was also searched as a keyword with a truncation operator when appropriate (eg, behavio*). Medical Subject Headings and keyword searches were conducted across all the databases except for Web of Science, where only keywords were used as topic terms.

Finally, we combined the results of previous searches, for example, *multiple sclerosis* AND *RCT* AND *motor activity*. All the searches were limited to articles in English. In total, 3903 citations were identified.

### Screening for Inclusion in the Full-Text Review

The full citations and abstracts for all 3903 studies were downloaded into EndNote, and duplicates were deleted (n = 715). Three reviewers (AF, EJB, and JP) screened the titles and abstracts of the remaining 3188 studies to identify citations for full-text review. We included studies of humans with MS and studies evaluating rehabilitation interventions using an RCT design. We excluded conference abstracts, dissertations, letters to the editor, protocols, studies reporting results of MS combined with other populations (eg, stroke), and studies in which the rehabilitation intervention was secondary or adjunctive to a medical intervention (eg, surgery or pharmaceutical treatment). All the citations were reviewed by at least two reviewers. When disagreements about inclusion/exclusion were encountered, discussions with the third reviewer occurred. If consensus could not be reached, the senior author (MF) made the final decision. Figure 1 is a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart showing the search and screening processes.

### Full-Text Review, Data Extraction, and Analysis

One of two authors (JP or JL) completed the full-text review and data extraction. Another author (AF or EJB) then verified the extraction. General study information was extracted from the articles: research questions/objec-

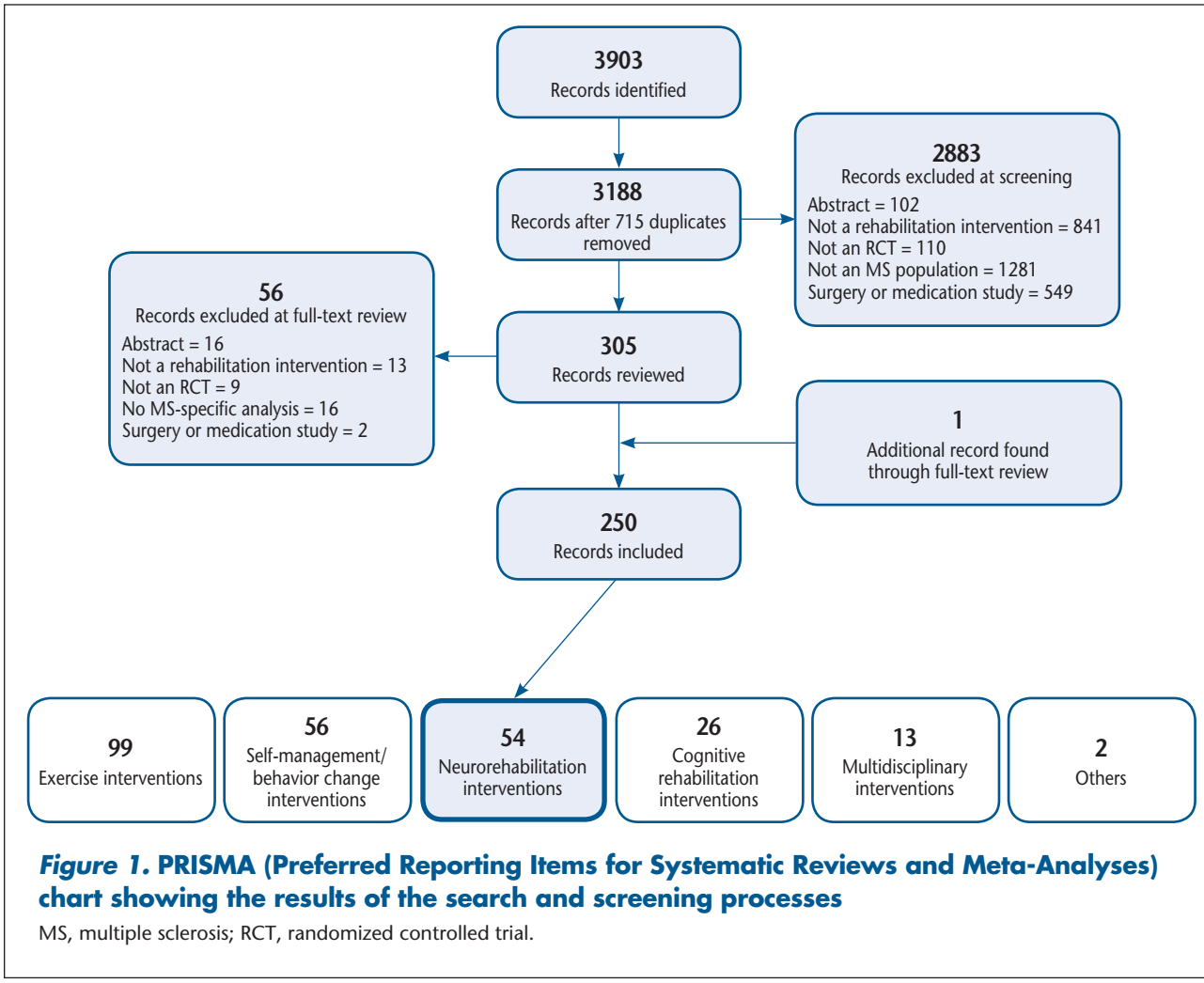


***Figure 1.* PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart showing the results of the search and screening processes**

MS, multiple sclerosis; RCT, randomized controlled trial.

tives, intervention description, sample size, age, percentage of females, and level of disability.

Two rehabilitation clinicians with experience delivering rehabilitation services to people with MS (AF and MF) grouped articles by type of intervention. These groupings were defined a priori by one clinician (MF) and then were confirmed and validated by the other clinician (AF). Groupings were determined by mechanism of the intervention rather than by outcomes based on the intervention description in the article. Six intervention groupings were identified: exercise (n = 99), self-management/behavior change (n = 56), cognitive rehabilitation (n = 26), multidisciplinary (n = 13), others (n = 2), and neurorehabilitation (n = 54). This article focuses on articles with neurorehabilitation interventions, which included six broad categories: robotics/technology-enhanced (eg, robot-assisted gait training) (n = 7), task-oriented training/neurorehabilitation principles (eg, the Bobath concept, task-oriented exercises) (n = 7), electrical stimulation (eg, functional electrical stimulation/neuromuscular electrical stimulation/noninvasive brain stimulation) (n = 12), temperature regulation (n = 6), magnetic field therapy (n = 5), and vibration (n = 9). In addition, we had a miscellaneous category of interventions (n = 8) that did not fit any of the other categories. Table 1 provides the definition of each category.

The included articles were scrutinized for information about comorbidities: if they were excluded/included, how they were reported and described, and whether their effect on the outcomes was tested.

## Results

Of the 54 RCTs, 40 excluded individuals with comorbidities, and only 2 reported on the comorbidity of enrolled participants, and neither of these examined comorbidity as a moderator or mediator of intervention outcomes. A summary of the reviewed studies follows, and Supplementary Table 1 (published in the online

**Table 1. Definitions of neurorehabilitation intervention categories**

| Intervention category | Definition |
|---|---|
| Robotics/technology-enhanced | Any studies that include an intervention that is enhanced by the use of technology. Technology includes the use of robotic systems and computer software or hardware. Robotics can be administered under the supervision of a therapist, providing intensive, task-oriented motor training of the patient's limbs. |
| Task-oriented training/ neurorehabilitation principles | Any studies that include an intervention that focuses on improving performance and skill in functional tasks through goal-directed practice and repetition. Also includes studies that focus on improving neuromuscular control using various strategies, eg, the Bobath concept and proprioceptive neuromuscular facilitation. |
| Electrical stimulation | Any studies that include an intervention that uses electrical current to modify neuromuscular activity and restore the ability to perform activities of daily living through electrical stimulation, neuromuscular electrical stimulation, transcutaneous electrical nerve stimulation, and functional electrical stimulation. |
| Temperature regulation | Any studies that use a variety of modalities to decrease the core body temperature. These systems can be passive or active. Active systems use a liquid cooling garment and a portable chiller or heat exchange unit. Passive systems use ice packs placed in pockets in a garment or the evaporation of water at room temperature as the heat exchange medium. |
| Magnetic field therapy | Any studies that include an intervention that uses a magnetic pulsing device to deliver electromagnetic waves. |
| Vibration | Any studies that include an intervention that uses a mechanical oscillatory motion provided through vibration of varying frequencies, amplitudes, and forces. Vibration may be defined as an oscillatory change in force, acceleration, and displacement with respect to time. The vibration can be applied to different body parts using specific joint angles for any limited time. |
| Miscellaneous | Any studies that involve ≥2 of the other categories or that do not fit into any of the other categories. |

version of this article at ijmsc.org) provides a summary of the study characteristics.

## Robotics/Technology-Enhanced Interventions

Three of seven RCTs had active comparison groups, and the remaining four had true control groups.[12-18] The number of intervention sessions ranged from 6[18] to 15[12] over 3[12,14,18] to 6[16,17] weeks. The duration of each session ranged from 30[12,13,15] to 60[16] minutes.

The sample size (per group) ranged from 6[18] to 26[13] participants. The mean age of the groups ranged from 47[15] to 61[13] years. Participants were mostly females (range, 43%–90%) with relapsing-remitting MS (RRMS) and minimal to severe disability measured using the Expanded Disability Status Scale (EDSS).

Six of seven studies (86%) reported the comorbidities of excluded individuals (Figure 2).[12-14,16-18] The most commonly excluded comorbidities were cognitive impairment (n = 5, 71%)[12,14,16-18] and any orthopedic or joint problems that limited range of motion (n = 4, 57%)[12-14,18] (Figure 3). Of the five studies that excluded cognitive impairment, only two provided information on the measurement tools and cutoff scores used to determine eligibility.[16,17] No studies provided details on the number of individuals excluded because of comorbidity. Furthermore, no studies reported on the comorbidities of enrolled participants or examined the possible mediating or moderating effect of comorbidities on intervention outcomes.

## Task-Oriented Training/Neurorehabilitation Principles

Four of seven studies (57%) had active comparison groups,[19-22] and the remaining three had usual care[23,24] or no intervention control groups.[25] The number of intervention sessions ranged from 10[25] to 24[24] over 2[25] to 8[24] weeks. The duration of each session ranged from 30[21] to 120[25] minutes.

The sample size (per group) ranged from 9[21] to 28[23] participants. The mean age of the groups ranged from 33[19] to 55[25] years. Participants were mostly females (range, 54%–83%) with RRMS and minimal to severe disability measured using the EDSS.

Four of seven studies (57%) reported the comorbidities of excluded individuals (Figure 2).[20,21,24,25] The most commonly excluded comorbidities were cognitive impairment (n = 4, 57%)[20,21,24,25] and psychiatric disorders (n = 3, 43%)[20,21,24] (Figure 3). These psychiatric disorders were not identified. Of the four studies that excluded cognitive impairment, only one provided information on the measurement tools and cutoff scores used to determine eligibility.[25]

No studies provided details on the number of individuals excluded because of comorbidity. Furthermore, no studies reported on the comorbidities of enrolled participants or examined the possible mediating or moderating effect of comorbidities on intervention outcomes.

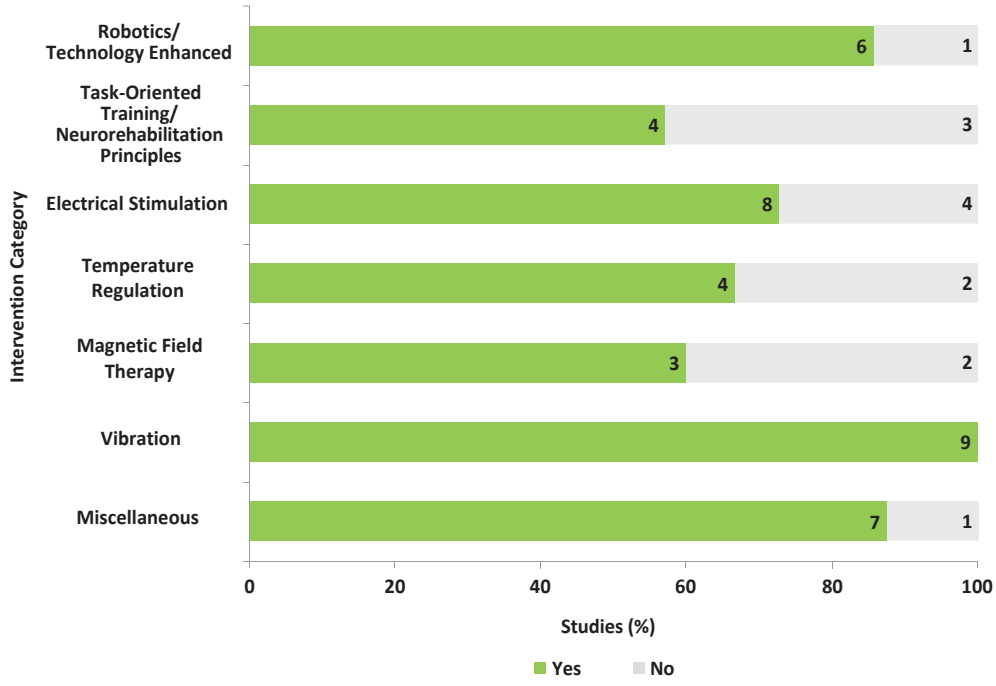


***Figure 2.* Studies excluding at least one comorbidity by intervention category**

Green bars represent the number of studies reporting at least one comorbidity as an exclusion criterion. Gray bars represent the number of studies that did not exclude any comorbidity.

## Electrical Stimulation Interventions

Of the 12 RCTs, 3 (25%) had active comparison groups[26-28] and 9 (75%) had sham treatment[29-36] or no intervention control groups.[37] The number of intervention sessions ranged from 10 to 112[33] over 5 days[29,32,36] to 24 weeks.[28] The duration of each session ranged from 15 minutes[32,36] to 24 hours.[27]

The sample size (per group) ranged from 9[29] to 36[31] participants. The mean age of the groups ranged from 38[34] to 57[26-28] years. Participants were mostly females (range, 30%–84%) with RRMS and minimal to severe disability as measured using the EDSS.

Eight of 12 RCTs (67%) reported the comorbidities of excluded individuals (Figure 2).[27,28,31-33,35-37] The most commonly excluded comorbidities were cognitive and psychiatric disorders,[27,28,31,32,35,37] and any other neurologic problems[27,32,33,36] (Figure 3). These psychiatric disorders and neurologic problems were generally not identified. No studies provided details on the number of individuals excluded because of comorbidity. Only one study reported the comorbidities of enrolled participants.[29] These comorbidities were anxiety and depression measured using a visual analogue scale and the Beck Depression Inventory, respectively. However, the possible mediating or moderating effect of comorbidities on intervention outcomes was not examined.

## Temperature Regulation Interventions

Four of six RCTs (67%) had no intervention or sham treatment control groups,[38-41] and the remaining two had both no intervention and no sham treatment groups.[42,43] The number of intervention sessions ranged from one[40] to three[42] over 1 day[40] to 4 weeks.[43] The duration of each session ranged from 20[38] to 60[42,43] minutes.

The sample size (per group) ranged from 6[42] to 22[40] participants. Most of the studies (n = 5, 83%) provided the mean age of the overall sample, ranging from 41[42] to 52[39] years. Participants were mostly females (range, 40%–86%) with minimal to severe disability as commonly measured using the EDSS.

Four of six RCTs (67%) reported the comorbidity of excluded individuals (Figure 2).[38,40,42,43] The most commonly excluded comorbidities were cardiovascular and pulmonary diseases (n = 3, 50%)[38,40,43] and other unspecified conditions (n = 3, 50%)[40,42,43] (Figure 3). No studies provided details on the number of individuals excluded because of comorbidity. Furthermore, no studies reported the comorbidities of enrolled participants or examined the possible mediating or moderating effect of comorbidities on intervention outcomes.

## Magnetic Field Therapy Interventions

All five RCTs had sham treatment groups rather than active comparison groups.[44-48] The number of intervention sessions ranged from 4[45] to 40[46] over 1[47] to 8[44,48] weeks. The duration of each session ranged from 16 minutes[46] to 24 hours.[48]

The sample size (per group) ranged from 15[48] to 34[45] participants. The mean age of the groups ranged from

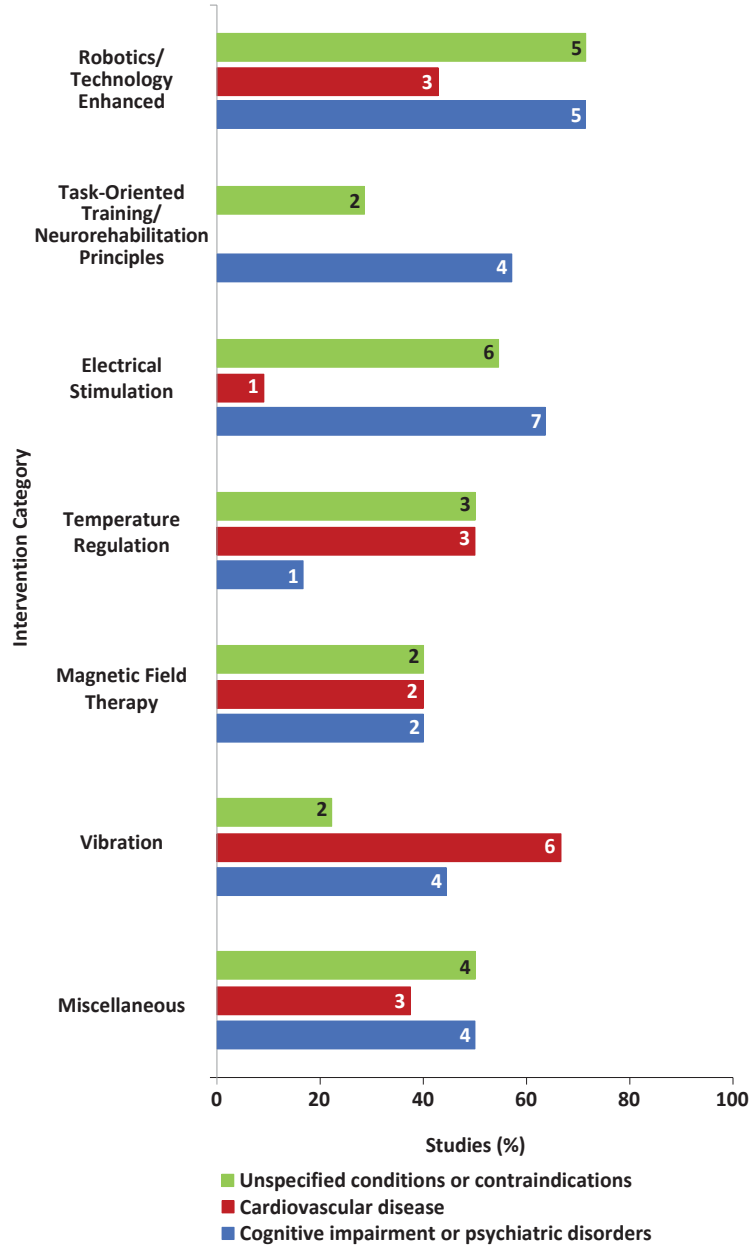


***Figure 3.* Most common comorbidities excluded by intervention category**

Cognitive impairment or psychiatric disorders includes depression, anxiety, and cognitive deficits. Cardiovascular disease includes recent myocardial infarction, heart disease, and implanted pacemaker. Unspecified conditions or contraindications includes generalized exclusion criteria, such as any other neurologic conditions, other conditions that may affect motor function, and any coexisting medical condition impairing gait or contraindicating treatment. The number of studies reporting at least one of these types of comorbidities is shown for each intervention category.

44[46,47] to 53[44] years. Participants were mostly females (range, 53%–73%) with RRMS and moderate to severe disability as measured using the EDSS.

Three of five RCTs (60%) reported the comorbidities of excluded individuals (Figure 2).[44,46,47] Across these studies, participants using pacemakers and those with cognitive impairment and other unspecified conditions were commonly excluded (Figure 3). No studies provided details on the number of individuals excluded because of comorbidity. Furthermore, no studies reported the comorbidities of enrolled participants or examined the possible mediating or moderating effect of comorbidities on intervention outcomes.

## Vibration Interventions

Three of nine RCTs (33%) had active comparison groups,[49-51] and the remaining six (67%) had control groups (ie, no intervention, including delayed entry or sham treatment).[52-57] The number of intervention sessions ranged from 9[54] to 24[50,51,53] over 3[54,57] to 20[52] weeks.

The sample size (per group) ranged from 5[50] to 30[54] participants. The mean age of the groups ranged from 34[53] to 55[49,55] years. Participants were mostly females (range, 57%–100%) with RRMS and minimal to severe disability as measured using the EDSS.

All nine studies reported the comorbidities of excluded individuals (Figure 2). The most commonly excluded comorbidities were cardiovascular problems (eg, thrombosis and the use of pacemakers),[50,51,53-56] epilepsy,[50,51,55,56] and psychiatric disorders[49,51,52] (Figure 3). These psychiatric disorders were not identified. No studies provided details on the number of individuals excluded because of comorbidity. Of the nine RCTs, only one reported the comorbidities of enrolled participants.[49] In this study, 4 of 42 participants were taking an antiepileptic medication. However, this study did not examine the possible mediating or moderating effect of comorbidities on intervention outcomes.

## Miscellaneous Interventions

Studies (n = 8) were included in this category if they did not fit any of the other categories (balance and gait, n = 1; massage, n = 3; and vestibular interventions, n = 1) or involved a combination of two or more categories (n = 3). Four of eight RCTs (50%) had active comparison groups[58-61]; two studies had active

comparison and waitlist or usual care control groups,[62,63] and the remaining two had no intervention or sham treatment control groups.[64,65] The number of intervention sessions ranged from 1[61] to 28[59] over 1[61] to 8[64] weeks. The duration of each session ranged from 15[59] to 60[60-62,64] minutes.

The sample size (per group) ranged from 8[60] to 25[65] participants. The mean age of the groups ranged from 36[63] to 59[59] years. Participants were mostly females (range, 33%–89%) with RRMS and minimal to severe disability as measured using the EDSS.

Seven of eight studies (88%) reported the comorbidities of excluded individuals (Figure 2). The most commonly excluded comorbidities were unspecified conditions or contraindications to participating in the intervention (n = 4, 50%)[62-65] and cognitive impairment and psychiatric disorders (n = 4, 50%)[58,60,64,65] (Figure 3). Of the four studies excluding participants with cognitive impairment and psychiatric disorders, only two provided information on the measurement tools and cutoff scores used to determine eligibility.[60,64] No studies provided details on the number of individuals excluded because of comorbidity. Furthermore, no studies reported the comorbidities of enrolled participants or examined the possible mediating or moderating effect of comorbidities on intervention outcomes.

## Discussion

Given the wide range of MS-related problems and the comprehensive rehabilitation approaches that are available to address them, it was not surprising to find 54 studies examining the effectiveness or efficacy of neurorehabilitation interventions. Although the issue of comorbidity was considered in most of these studies (n = 40, 74%), it was limited to excluding individuals from participating in the trials. Of concern is the finding that most of the commonly excluded comorbidities represent some of the most prevalent ones experienced by people with MS (eg, cognitive and psychiatric disorders and cardiovascular diseases).[6] Furthermore, in some studies, the descriptions provided for excluded comorbidities were vague, for example, "other illnesses that may affect motor function."[16]

Most studies did not provide any information about measurement tools and cutoff scores used to determine eligibility, particularly for cognitive impairment. Therefore, it is unclear what the nature and potential cause of the excluded impairments are (eg, executive functioning, attention, memory, dementia, and MS). This lack of detail means that we may be misclassifying some studies in this review (ie, classifying as comorbidity when it is MS related), although all readers would have the same challenge. The lack of detail is also a challenge for future replication and reduces reader confidence in knowing to whom the intervention results can be generalized.

Researchers in MS tend to exclude individuals with comorbidities in neurorehabilitation trials for several reasons. First, researchers usually attempt to maximize participant safety and reduce the risk of adverse events during trials. Although participant safety is a critical concern, excluding individuals with comorbidities may lead to an inaccurate safety evaluation of some interventions, which may have implications for clinical practice. The practice of excluding people with comorbidities from neurorehabilitation trials means that we have limited knowledge about the clinical safety of these interventions for a large proportion of people with MS.

Second, researchers usually work to maximize the internal validity of their studies by creating homogeneous samples and reducing the risk of confounding. Excluding individuals with comorbidities helps in these efforts. However, in achieving greater internal validity, external validity is compromised, and the applicability of results to routine clinical settings becomes questionable. In clinical practice, rehabilitation care is provided to people with MS who typically have comorbidities that could influence their clinical presentation and management. Furthermore, the exclusion of people with comorbidities limits our understanding of how these conditions may be contributing to differential adherence or treatment effects and may also be limiting our ability to tailor interventions for the "whole" person. Studies in people with other chronic neurologic conditions, such as stroke, have shown that comorbidity can affect treat-

### PracticePoints

- Investigations of neurorehabilitation interventions in MS tend to exclude individuals with comorbidities, making it difficult to generalize the findings to large segments of the MS population.
- Without information about the comorbidities experienced by participants with MS, the effect on study outcomes cannot be determined.
- Although including people with MS who have comorbid conditions will create more heterogeneous samples, taking this methodological risk is likely to provide more generalizable knowledge about the efficacy and effectiveness of neurorehabilitation interventions.

ment outcome, adherence, and maintenance of the treatment effect.[66,67]

To find a balance between the advantages and disadvantages of including people with comorbidities in neurorehabilitation trials, MS researchers need to start moving toward large multisite pragmatic trials that include a wider range of participants. Despite the complexity of these studies, such a design will maximize applicability and generalizability and provide opportunities for conducting subgroup analyses involving people with MS with comorbidities.[68]

Despite the growing interest in comorbidities in people with MS, knowledge of their effect on common MS treatments remains in its infancy, even among more traditional pharmacologic interventions.[68] This review found that knowledge about the effect of comorbidity on neurorehabilitation outcomes in people with MS is almost nonexistent. Despite reviewing 54 RCTs, we found only two studies that reported the comorbidities of enrolled participants. However, neither of these studies examined the possible mediating or moderating effect of comorbidities on intervention outcomes. Recent systematic reviews have identified common comorbidities experienced by people with MS.[6] Together with the gaps identified by the present review, the body of evidence suggests that MS neurorehabilitation researchers should prioritize the inclusion of participants with comorbidities such as cognitive impairment and psychiatric and cardiovascular conditions. This work also suggests that investigating the effect of these comorbidities on intervention outcomes is clearly warranted.

This review has some limitations that warrant consideration. First, scoping reviews usually include a wider spectrum of evidence gathered from various sources, for example, electronic databases and gray literature. The search strategy for this review was limited to electronic databases and peer-reviewed journal articles. Second, we focused on RCTs without including other designs. Although RCTs are considered the gold standard, the strategy reduced the number of included studies for this review.

## Conclusion

Despite the limitations, this review documents important gaps in knowledge about the effect of comorbidity on neurorehabilitation outcomes and identifies a critical need for future studies to address this issue. This knowledge is needed so that clinicians can make evidence-based treatment decisions. Without this information, we will be limiting our understanding of the mechanisms of comorbidity and its effect on relevant clinical and research outcomes specific to neurorehabilitation. □

**Financial Disclosures:** The authors have no conflicts of interest to disclose.

**Funding/Support:** Ms. Fakolade was supported in part by a Multiple Sclerosis Society of Canada Doctoral Studentship. Dr. Bisson was supported by a National Multiple Sclerosis Society Mentor-Based Postdoctoral Fellowship.

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