Behavioral Interventions to Improve Sleep Outcomes in Individuals With Multiple Sclerosis: A Systematic Review

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ABSTRACT

BACKGROUND: Sleep disturbances are common in individuals with multiple sclerosis. The objective of this systematic review was to determine effective behavioral interventions to improve their sleep.

METHODS: Literature searches were performed in December 2021 in Ovid MEDLINE, Elsevier Embase, and Web of Science, along with hand searching for grey literature and cited references. Four reviewers independently reviewed titles and abstracts (2 reviewers for each article; n = 830) and the full-text articles (n = 81). Consensus for inclusion was achieved by a fifth reviewer. Thirty-seven articles were eligible for inclusion. Four reviewers extracted relevant data from each study (2 reviewers for each article) using a standard data extraction table. Consensus was achieved for completeness and accuracy of the data extraction table by a fifth reviewer. The same 4 reviewers conducted a quality appraisal of each article to assess the risk of bias and quality of the articles, and consensus was achieved by a fifth reviewer as needed. Descriptive data were used for types of interventions, sleep outcomes, results, and key components across interventions.

RESULTS: Overall, the cognitive behavioral therapy for insomnia, cognitive behavioral therapy/psychotherapy, and education/self-management support interventions reported positive improvements in sleep outcomes. Quality appraisal scores ranged from low to high, indicating potential for bias.

CONCLUSIONS: Variability in the intervention type, intervention dose, outcomes used, training/expertise of interventionist, specific sample, and study quality made it difficult to compare and synthesize results. Further research is necessary to demonstrate the efficacy of most of the interventions.

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Nearly 1 million people in the United States are living with multiple sclerosis (MS), and disturbed sleep is a very common challenge in this population.[1] Sleep problems are significantly more common in people with MS (~70%) than in the general population[2]; however, the incidence is likely higher because sleep disorders in individuals with MS are severely underdiagnosed.[3]

Common contributors to sleep disturbances in people with MS include nocturia, muscle spasticity, depression, anxiety, and pain.[4] Furthermore, neuropathology due to MS may have a direct physiological effect on circadian rhythm,[5] and adverse effects from medications can also have a significant effect on sleep, further complicating treatment.[4] Sleep disturbances in people with MS have been associated with poorer cognitive performance, lower quality of life, higher disability, and increased prevalence of pain, fatigue, depression, anxiety, and sexual and bladder dysfunction.[6,7] Because of the overlapping symptoms of MS and disturbed sleep, poor sleep in people with MS is a complicated issue.

Various pharmacologic and lifestyle/behavioral interventions have been studied to address sleep disturbances in people with MS. Although pharmacologic interventions are appropriate in certain cases, medication can have adverse effects (ie, sedation, dizziness, cognitive impairment, motor incoordination) and concerns for long-term use, including exacerbation of sleep disturbances and insomnia.[8] Conversely, behavioral interventions for MS are safe for short- and long-term use, have had a promising effect on sleep issues, may be more accessible, and may potentially modify the disease process.[9] Behavioral interventions that have been effective, durable, and safe include cognitive behavioral therapy for insomnia (CBT-I), physical activity, mindfulness training, education, and psychotherapy; however, the effective components of sleep interventions for people with MS have yet to be summarized.

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The body of research examining behavioral interventions to improve sleep in people with MS is large and rapidly expanding; thus, the literature in the field has been assembled for close examination to determine which are effective. It is anticipated that this systematic review will act as a guide for clinical practice and future research in this burgeoning field by identifying efficacious behavioral interventions to enhance sleep as well as gaps in knowledge.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to identify the standards of this review protocol. This systematic review was registered with PROSPERO, an international prospective register of systematic reviews. Ovid MEDLINE, Elsevier Embase, and Web of Science were used to identify relevant studies. Keywords and database-provided controlled vocabularies were used in Embase and MEDLINE, along with various search techniques and Boolean operators. Web of Science was searched using keywords only. Search terms included *multiple sclerosis*, *sleep*, *sleep wake disorders*, *circadian rhythm*, *exercise*, and *exercise therapy* (**TABLE S1**, available online at IJMSC.org). To include nonpharmaceutical intervention outcomes of sleep quality, terms such as *behavioral therapy*, *complementary therapy*, *mind-body therapy*, *muscle relaxation*, *qigong*, *mindfulness*, *meditation*, and others were also searched. Publication language filters were not applied. Additional resources (eg, ClinialTrials.gov, Google Scholar) were used to identify relevant grey literature. Searches were performed between December 1 and 28, 2021.

Studies were included in the systematic review if they (1) involved the study of humans diagnosed as having MS, (2) had an intervention study design (ie, pre-post test, randomized and nonrandomized trial study design), (3) included lifestyle or behavioral interventions, and (4) included sleep as an outcome. Studies were excluded from the systematic review if they (1) included the study of animals, (2) involved any other neurologic condition, (3) were written in a language other than English, (4) had a nonintervention study design (reviews, opinions, editorials, protocols, cross-sectional, observational), (5) contained a duplicate data set (same data reported in >1 study), or (6) were irrelevant to our objectives.

Each title/abstract was independently reviewed by 2 of 4 reviewers (D.T., S.J.D., S.L.C., C.S.) and determined as eligible/ineligible based on the inclusion/exclusion criteria. Discrepancies were resolved by a fifth reviewer (J.W.) to reach consensus. Then the full-text manuscripts were reviewed for eligibility, and, again, consensus was reached on discrepancies by the fifth reviewer.

Data were extracted from the full-text articles by both a primary reviewer and a secondary reviewer using a standardized data extraction spreadsheet and included the first author, publication year, study country, study design, study objective, number of participants, number of dropouts, participant information (ie, age, MS type and severity, disease duration, specific impairment[s] for eligibility), intervention information (ie, type, dose, interventionist, setting, study assessment time points, control group [if included]), primary and sleep outcomes, and sleep-specific results. Consensus was reached on discrepancies by the fifth reviewer.

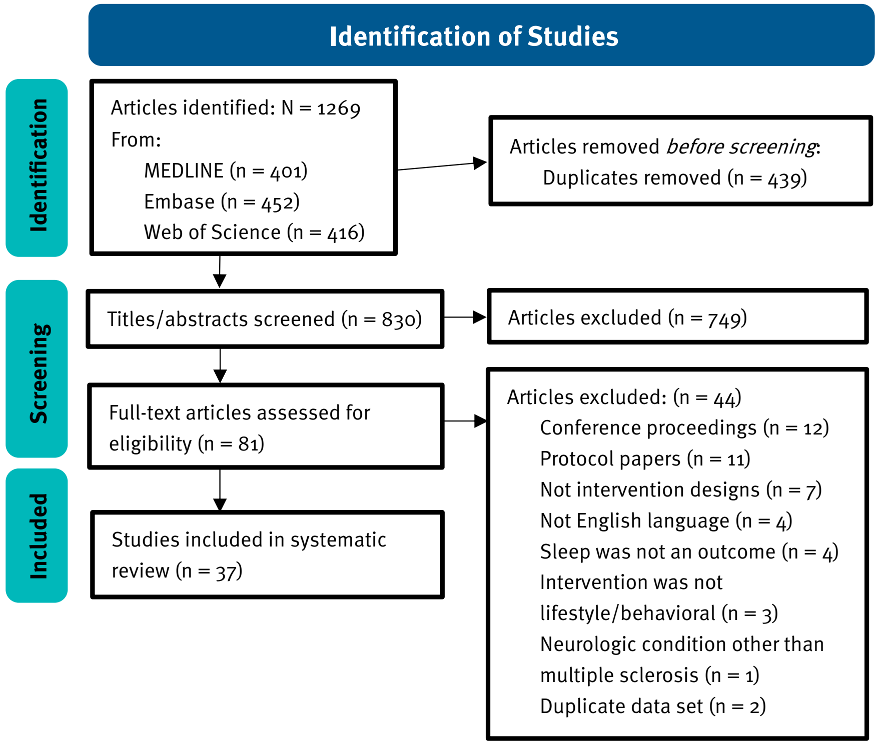
To assess the risk for potential bias and the quality of the included articles, critical appraisals were independently conducted by 4 reviewers (2 for each article; same reviewers who conducted data extraction), and discrepancies were resolved by the fifth reviewer. Five different quality appraisal tools were used according to article types: the National Heart, Lung, and Blood Institute quality assessment for before-after (pre-post) studies with no control group[10] and the Joanna Briggs Institute's (JBI) critical appraisal checklists for randomized controlled trials (RCTs), case reports, quasi-experimental studies, and qualitative research.[11] Overall quality scores were then calculated for each study as follows: "yes" = 2, "unclear" and "cannot determine" = 1, and "not reported" or "no" = 0, and a percentage score was calculated.[12] A score of 100% indicates the highest possible quality score and demonstrates the quality of the study design and implementation to reduce potential bias. Because question 12 was rated as "not applicable" for all the pre-post study design articles, the denominator was adjusted (ie, 11 × 2 rather than 12 × 2) to calculate overall percent quality score. Also, in the case series quality appraisal, 2 questions were deemed "not applicable," so the denominator was also adjusted (ie, to 8 × 2 rather than 10× 2). To be consistent with other checklists, a "not reported" option was added to the JBI RCT checklist. Only 1 reviewer conducted quality appraisal for the qualitative research studies because of her expertise in qualitative design (S.J.D.). Because there is not a specific checklist for pilot RCTs, the JBI RCT appraisal checklist was used for studies that self-identified as a pilot RCT.

RESULTS

The search strategy generated 1269 total citations. There were 439 duplicates removed, leaving 830 unique results. Subsequent title/abstract review excluded 749 studies, leaving 81 studies for full-text review. After full-text review, 44 studies were excluded, leaving 37 studies for data extraction and quality appraisal (**FIGURE 1**).

The studies that met the inclusion/exclusion criteria for this systematic review are summarized in **TABLE S2** (organized by intervention type and by study design). Studies were conducted in North America (48.6%, of which 94% were in the United States), Europe (29%), Asia (23%), and Australia (3%). The most prevalent study design was RCT (n = 19,[13-31] of which 9[23-31] self-identified as a pilot RCT [54%]), followed by single-group pre-post design (n = 11[32-42] [31%]). Case reports (n = 2[43,44] [6%]), qualitative studies (n = 2[45,46] [6%]), quasi-experimental studies (n = 2[47,48] [6%]), and case series (n = 1[49] [3%]) were also included. Four of the studies included are secondary analyses,[14,45,46,50] of which two[46,50] analyzed data from a primary study also included in this systematic review.[29,47]

FIGURE 1. Study Identification



Sample sizes ranged from 1[43,44] to 218[16] individuals, and 1565 individuals were included in total. Participants in all the studies were adults ranging in age from 34.3 years[13] to 60.1 years.[37] Relapse-remitting MS constituted most MS types for every study except 3.[26,38,44] Sleep was stated as the primary outcome in 9[13,14,19,23,28,30,32,33,37] of the 37 studies. The Pittsburg Sleep Quality Index (PSQI) was the most commonly used sleep outcome (n = 19[13,16-18,22-26,28,29,31,35,37,40-42,44,47]), followed by the Insomnia Severity Index (ISI) (n = 10[19-21,24,26,29,31,32,43,49]), actigraphy (n = 5[24,25,30,33,47]), and sleep log/diary data (n = 5[25,30,33,43,44]). An objective measurement was incorporated into 6 of the studies (actigraphy [n = 5[25,30,33,43,44]] and electroencephalography [n = 1[32]]). Interventions included physical activity (n = 13[18-20,24-26,28,32,33,37,38,40,42]), CBT-I (n = 6[29-31,43,44,49]), CBT/psychotherapy (n = 3[13,14,17]), mindfulness/relaxation (n = 6[15,35,36,45-47]), education and self-management support (n = 4[16,23,41,48]), and complementary and alternative interventions, including acupuncture,[34] neurofeedback and hypnosis,[51] trauma-releasing exercises,[39] foot reflexology,[22] and integrated imaginative distention.[21] Details regarding sample demographics, intervention provided, and the major sleep findings are summarized by intervention category in **TABLE S3**. Results of the studies are summarized and described next by intervention category.

Physical Activity

Thirteen[20,24-26,28,32,33,37,38,40,42] of the 37 studies incorporated physical activity as a behavioral intervention. A variety of physical activity interventions were used, including resistance training,[33] aerobic exercise,[19,24,28,32] general individualized exercise programs,[26,37] physical activity lifestyle interventions,[18,25,40] yoga,[42] exoskeleton assisted walking,[38] and aquatic exercise.[20] Five of the physical activity studies had sleep as a primary outcome[19,28,32,33,37]; of these, 3 were single-group pre-post studies[32,33,37] and 2 were RCTs[28,51] (1 self-identified pilot RCT[28]).

All 4 pilot physical activity RCTs had statistically significant improvement in sleep outcomes (effect sizes ranging from small to large).[24-26,28] Siengsukon et al[28] was the only pilot physical activity RCT in which sleep was explicitly included as the primary outcome. They reported that both the 12-week moderate-intensity aerobic exercise group and the low-impact walking and stretching group experienced large significant improvements in PSQI scores, with no significant between-group difference; however, a significant between-group difference was found on the Epworth Sleepiness Scale (large effect).

Cederberg and Motl[25] reported on a sample of individuals with MS and restless legs syndrome. After a 16-week physical activity intervention, they observed significant positive effects on the International Restless Legs Syndrome Study Group rating scale score, restless legs syndrome severity during the night and during the day while resting and while active, sleep satisfaction, self-reported time in bed, and total sleep time compared with the waitlist control. In addition, other sleep outcomes demonstrated moderate to large effect sizes but were not statistically significant.

Al-Sharman et al[24] reported that a 6-week moderate-intensity aerobic exercise group had significant moderate to large improvements in PSQI global scores, ISI scores, sleep efficiency, and wake time after sleep onset assessed via actigraphy compared with a home exercise group. Furthermore, a change in serotonin level was significantly correlated with change in PSQI score in the aerobic exercise group.

Grubić-Kezele et al[26] reported a significant large improvement on the ISI after an 8-week individualized exercise program compared with socializing at the MS Society center. The only PSQI measure that showed a significant large improvement was daytime sleep dysfunction. In addition, other sleep outcomes demonstrated small to large effect sizes but were not statistically significant.

Two RCTs reported medium effect sizes for ISI change after 8-week endurance and coordinative training[51] and 8-week, twice weekly aquatic exercise.[20] Neither study provided group statistical comparisons. In a third RCT,[18] there was a moderate nonsignificant improvement in PSQI scores in the group that participated in a 24-week internet behavioral intervention to increase lifestyle physical activity, and no significant between-group differences were reported.

Three of the 6 single-group pre-post physical activity studies stated sleep as a primary outcome. Jeong et al[37] reported a slight worsening of PSQI scores from baseline to 3 months of a daily, individualized, at-home exercise intervention. Three weeks of endurance and physiotherapy sessions significantly improved ISI scores, sleep-onset latency, sleep efficiency, and wake after sleep onset, according to Sadeghi Bahmani et al.[32] Andreu-Caravaca et al[33] demonstrated improvements in sleep efficiency (via actigraphy) and quality, comfort, feeling of rest, and ease of falling asleep (via Karolinska Sleep Diary) after resistance training sessions compared with nontraining sessions.

In the other 3 single-group pre-post physical activity studies, sleep was not the primary outcome or it was unclear whether sleep was a primary outcome. Vasudevan et al[42] reported nonsignificant improvement in the PSQI score using a 12-week personalized yoga program. Mehrabani et al[40] reported significant improvement in sleep quality immediately after a 15-week physical activity intervention; however, the improvement was not sustained 7 weeks after the intervention. The 8-week study by Kozlowski et al[38] on exoskeleton-assisted walking reported mixed results using the Quality of Life in Neurological Conditions sleep disturbance scale.

CBT-I

Six[29-31,43,44,49] of the 37 studies incorporated a CBT-I intervention, and all reported improved sleep outcomes. Three were pilot RCTs,[29-31] of which 1 was a secondary analysis.[30] Two of the CBT-I studies were case reports,[43,44] and 1 was a case series.[49] Sleep was stated as the primary outcome in only the secondary analysis.[30]

In the 2 pilot RCTs by Siengsukon et al, the 6-week web-based CBT-I[31] and 6-week in-person CBT-I[29] interventions produced significant large improvements in PSQI, ISI, and Sleep Self-Efficacy scores. The secondary analysis by Williams-Cooke et al[30] of the in-person CBT-I study revealed sleep log data with significant moderate to large improvements in sleep efficacy and a reduction in time in bed and variability in sleep efficacy. Actigraphy data from the CBT-I group demonstrated a significant large reduction in time in bed and total sleep time from baseline to after the intervention, and the active control group showed a significant increase in variability in sleep efficiency.

Both individuals involved in the case reports demonstrated improved sleep outcomes. Loveless et al[43] reported on a man in his mid-50s with relapse-remitting MS. After 13 CBT-I sessions, the patient's sleep log demonstrated increases in sleep efficiency (from 29.0% to 74.49%) and total sleep time (from 2.69 to 5.86 hours) and decreases in sleep latency (from 145 to 60 minutes), wake after sleep onset (from 240 to 60 minutes), and early morning awakenings (from 110 min to 0 min). The case report by Majendie et al[44] involves a 40-year-old man with secondary progressive MS and sleep disturbance. His PSQI global score improved from 10 to 5 after 8 sessions of CBT-I, and 7 months after treatment it was reported to be a 1. Sleep-onset latency, sleep duration, and sleep efficiency also improved, and the participant implemented a medication withdrawal plan during his intervention time frame. In the case series by Clancy et al,[49] 86% of participants

PRACTICE POINTS

Intervention studies of cognitive behavioral therapy for insomnia, cognitive behavioral therapy/psychotherapy, and education/self-management support reported positive outcomes.

The physical activity, mindfulness/relaxation, and complementary and alternative intervention studies reported mixed results.

Future research should focus on tailoring the intervention to the specific sleep issue, the intervention dose, consensus on sleep outcome measures, adequate statistical power, including an appropriate comparison group, ensuring adequate training of interventionists, intervention fidelity, and appropriate blinding. ■

reported improvements in both ISI scores and total sleep time after an average of 8 CBT-I sessions.

CBT/Psychotherapy

Three studies incorporated CBT/psychotherapy without a mindfulness focus.[13,14,17] All were RCTs, 1 of which was a secondary analysis[14]; 2 studies[13,14] stated sleep as the primary outcome.

Kiropoulos et al[17] compared 8 weeks of CBT with "treatment as usual" (medical care from their neurologist) and found group differences in PSQI scores immediately after the intervention and at the 20-month follow-up. Abbasi et al[13] reported significant differences in sleep quality between the group that received 8 sessions of CBT and a control group at the postintervention and 1-month follow-ups. The study by Baron et al[14] was a secondary analysis of a study by Mohr et al[52] and reported a decline in reported insomnia from 78% as baseline to 43% after treatment by telephone psychotherapy for depression.

Mindfulness and Relaxation

Six studies incorporated mindfulness and/or relaxation.[35,36,45-47,53] None had sleep as the primary outcome. One study was an RCT,[53] 2 were single-group pre-post studies,[35,36] 1 was a quasi-experimental study,[47] and 2 were qualitative studies consisting of secondary analyses.[45,46]

At the postintervention evaluation, the RCT by Cavalera et al[15] reported a strong effect on the Medical Outcomes Study Sleep Scale after an 8-week online mindfulness meditation intervention compared with an online psychoeducation control group; however, there was no statistically significant difference between groups after 6 months.

The 6-week single-group pre-post progressive muscle relaxation study by Dayapoğlu and Tan[35] demonstrated PSQI global score improvement after the intervention and significant improvement in the PSQI subscale scores of subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorder, and daytime dysfunction. The single-group pre-post study by Hoogerwerf et al[36] reported a small, nonsignificant difference on Symptom Checklist-90 scores before, after, and at 3-month follow-up of an 8-week mindfulness-based cognitive therapy intervention.

The intervention group in a quasi-experimental study by Lorenz et al[47] showed a moderate to large pre-to-post effect on sleep behaviors (not significant), sleep efficiency (significant), and total sleep time (not significant) after an 8-week mindfulness-based stress reduction course, although both the intervention and control groups had significantly reduced awakenings. There were no statistically significant differences between groups on sleep outcomes after the intervention; however, there was a small, nonsignificant effect on total sleep time and sleep behavior. Also, a 1-way repeated-measures analysis of variance that included baseline, postintervention, and 3-month postintervention data suggested a nonsignificant small to medium effect on self-reported sleep quality and sleep behaviors. Sessanna et al,[46] in a qualitative secondary analysis of the Lorenz et al study,[47] reported that the formats of the sleep retraining program were acceptable and provided an effective mode of delivery for adults with MS. The qualitative secondary analysis by Simpson et al[45] of an 8-week mindfulness-based stress reduction study[54] found that improved sleep was commonly reported.

Education and Self-Management Support

Four studies focused on MS education/fatigue management.[16,23,41,48] One had sleep as a primary outcome.[23] Two were RCTs[16,23] (of which 1 self-identified as a pilot RCT[23]), 1 used a single-group pre-post study design,[41] and 1 was a retrospective medical record review.[48]

The RCT by Hugos et al[16] compared two 6-week group programs, one a multicomponent fatigue management program and the other an MS education program (control). Although there was no significant change in PSQI score at program completion or at the 3-month follow-up, there was a significant improvement at the 6-month follow-up in the fatigue management group compared with the control group; however, PSQI scores remained poor (>5) at the 6-month follow-up. Akbarfahimi et al[23] conducted a pilot RCT of an occupational therapy–based sleep intervention and found that sleep quality significantly improved in the intervention group compared with the control group.

Sauter et al[41] conducted a single-group pre-post study assessing the impact of a fatigue management intervention and reported that the PSQI global score significantly improved after the 6-week course and remained improved after 7 to 9 months; the sleep efficiency component score was also significantly improved at 7 to 9 months. Participants were initially divided into a "treatment first" group or a "waitlist then treatment" group; however, all participants were included in the pre-post intervention statistical analyses. The retrospective study[48] reported significant improvement in sleep disturbances after a 3- to 4-session individualized cognitive rehabilitation program; however, no between-group comparison was conducted.

Complementary and Alternative Interventions

Five studies used complementary or alternative interventions to address sleep issues, including acupuncture,[34] neurofeedback and mindfulness used in conjunction with hypnosis,[51] trauma-releasing exercises,[39] foot reflexology,[22] and integrated imaginative distention.[21] None included sleep as a primary outcome. Three were RCTs[21,22,51] (1 of which self-identified as a pilot RCT[51]), and 2 used a single-group pre-post study design.[34,39]

The RCT by Sajadi et al[22] reported a significant difference in sleep quality between a group that participated in foot reflexology and a placebo group after the intervention; however, the intervention group's average PSQI score was significantly worse than the control group's PSQI score at baseline. No significant difference in ISI change scores between the integrative imaginative distention intervention group and the waitlist control group was reported by the RCT by Sgoifo et al.[21] In the pilot RCT[51] by Jensen et al, participants received an intervention with neurofeedback and hypnosis, mindfulness and hypnosis, or hypnosis alone (control). There was a large nonsignificant time × condition effect for sleep disturbance ($P = .17$; $\eta 2p = 0.15$). A large, significant time effect for neurofeedback/hypnosis was maintained at the 1-month reassessment, and a large, nonsignificant time effect for mindfulness/hypnosis was not maintained at the 1-month reassessment.

During the 9-week intervention, the trauma-releasing exercise training implemented by Lynning et al[39] led to a significant increase in participants' sleep quality based on a daily self-report measure. Becker et al[34] reported a significant improvement in Patient-Reported Outcomes Measurement Information System sleep disturbance scores after acupuncture and health promotion education.

Quality Assessment

The details of the quality appraisal analyses are reported in **TABLE S4**. The quality score for the 12 RCTs ranged from 35% to 73%, the 7 pilot RCTs ranged from 31% to 54%, the 2 quasi-experimental studies were 50% and 67%, and the 11 pre-post single-group design studies ranged from 27% to 64%. The quality scores for the 2 case reports were 50% and 88% and for the 2 qualitative studies were 70% and 80%. The quality score for the case series was 81%.

DISCUSSION

This is the first study to systematically review behavioral interventions to improve sleep in people with MS. The variability in the intervention type, dose, outcomes used, training/expertise of the interventionist, specific sample included, and quality of the study made it difficult to compare and synthesize results. Overall, the CBT-I, CBT/psychotherapy, and education/self-management support intervention studies reported positive outcomes, and the physical activity, mindfulness/relaxation, and complementary and alternative intervention studies reported mixed results. The quality appraisal scores ranged from low to high, indicating potential for bias. Although this systematic review suggests that many of the interventions are feasible and have a positive effect on sleep in people with MS, further research is necessary to demonstrate the efficacy of most of the interventions. Future research should focus on tailoring the intervention to the specific sleep issue, the intervention dose, consensus on sleep outcome measures, adequate statistical power, including an appropriate comparison group, ensuring adequate training of interventionists, intervention fidelity, and appropriate blinding.

Only 9 of 37 studies (24%) explicitly stated sleep as a primary outcome. Depression, fatigue, and feasibility were frequent primary outcomes. This illustrates the lack of behavioral interventions designed to specifically target sleep in people with MS. What may have contributed to the lack of sleep as a primary outcome is that many of the interventions themselves were not designed to target sleep specifically. The exception is CBT-I, a multidimensional intervention to treat insomnia, which likely explains the consensus in improved sleep outcomes in people with MS in the CBT-I studies. A recommended first-line treatment for insomnia, CBT-I addresses behaviors and thoughts that can negatively impact sleep.[55] The other interventions (eg, mindfulness, relaxation, complementary and alternative interventions) are less likely to target specific sleep impairments or disturbances and instead target secondary contributors to sleep.

The physical activity intervention studies had mixed results (8 positive; 3 positive results although not statistically significant; 2 had minimal to no change in sleep outcomes) due to extensive studies showing that physical activity has a positive effect on various sleep outcomes in the general population.[56] There are several possible explanations as to why physical activity had mixed results on sleep outcomes in people with MS: the studies were underpowered, the intervention lacked a sufficient dose of physical activity to positively affect sleep, sleep impairment was not a requirement for eligibility, a larger percentage of individuals with more progressive disability were in the sample. Although the exact mechanisms for how physical activity improves sleep are not clear, a possible mechanism is that the rise in body temperature leads to the self-induced internal cooling processes that initiate sleep.[57] Perhaps the rise in body temperature does not trigger the same internal cooling processes due to the heat sensitivity of people with MS or perhaps other MS symptoms (eg, spasticity, pain) mediate the effect on sleep. Additional research is needed to elucidate whether physical activity does indeed have a positive effect on sleep outcomes for individuals with MS, and if not, why.

Another challenge with synthesizing the results is that the outcomes used to assess sleep were often not valid or reliable measurements of sleep. For example, the primary construct assessed by the Quality of Life in Neurological Conditions sleep disturbance scale and the Hamilton Depression Rating Scale is a construct associated with sleep; however, these assessments appeared multiple times throughout the review and were sometimes the sole sleep outcome measure. Also, interestingly, only 6 of the included studies (16%) used an objective measure of sleep (eg, actigraphy, electroencephalography), and no study used polysomnography. Although objective measures reduce potential bias and assess certain constructs of sleep, they are typically more time-consuming and more costly. Perhaps because of the number of preliminary studies, the studies with sleep as a secondary outcome, or the studies' ease of administration, many in this review used self-report sleep assessments. Because objective and self-report sleep measures assess different sleep constructs, both types aid in understanding the effects of behavioral interventions. Moving forward, studies to assess the impact of behavioral interventions on sleep should use valid and reliable measurements that are specific to the intended sleep outcome, such as the PSQI to assess self-reported sleep quality, the ISI to assess insomnia severity, actigraphy to objectively assess the sleep/wake cycle, and polysomnography to assess sleep stages.

Most studies (78%) assessed immediate change in sleep due to the intervention, and only 9 studies[13,15-17,27,36,40,41,47] included longer-term follow-up (range, 1 month[13,27] to 7-9 months[41]). Importantly, 3 of these studies demonstrated sleep improvements immediately after the intervention that were not maintained at long-term follow-up.[13,17,41] Also, 1 study did not show positive improvement in sleep at the postintervention or 3-month follow-up but did show improvement in sleep at the 6-month follow-up.[16] These findings illustrates the importance of long-term tracking to determine maintenance (or lack thereof) of improvement in sleep outcomes (suggesting changed behavior) or that the impact of a sleep intervention may take time to become apparent. Future studies should include delayed reassessments to determine maintenance of improvement or evolution of change in sleep. In addition, because half of the studies that demonstrated initial improvement in sleep failed to maintain improvement at reassessment, future research should consider emphasizing behavior change theories and techniques.

The quality appraisal that was completed as part of this systematic review highlights limitations and potential biases of the studies included in this review. Many of the studies lacked blinding for participants, interventionists, and/or outcome assessors. Many of the RCTs did not include a power analysis, and the sample sizes were often small, which limits the interpretation of the results. Numerous studies had participants who dropped out, and an analysis of the impact of attrition was often absent. These findings reveal the potential for bias in the articles included, and, thus, conclusions and interpretation of the results should be viewed with this in mind.

We acknowledge that the JBI critical appraisal checklist for RCTs was used to assess the quality of the self-identified pilot RCTs, which likely resulted in a lower quality score for the pilot RCTs. The systematic review team made this decision after thoughtful discussion and after being unable to locate a critical appraisal checklist specifically for pilot RCTs. Pilot RCTs are used to determine feasibility or effect size, whereas RCTs are used to determine efficacy or effectiveness, and there is a debate as to whether pilot studies should assess treatment effects or group differences.[58] A critical appraisal checklist specific for pilot RCTs is necessary, and the determination of "pilot" should be made a priori and in accordance with the purpose and design of the study trial. Another note on the importance of language precision: there was often a lack of clarity whether the reported MS disease duration was from diagnosis or from symptom onset. This is an important distinction because it can be years from symptom onset to an actual physician diagnosis of MS.

Overall, this systematic review has summarized the current state of the literature on behavioral interventions for sleep in individuals with MS and suggests that additional well-designed research with the specific intention of assessing the impact of behavioral interventions on sleep using valid and reliable sleep measures in people with MS is warranted. The conclusions in this review and future research identified from this review will aid in guiding clinical practice centered around improving sleep in people with MS. ■

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