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REVIEW ARTICLE

Efficacy of interventions for improving health in patients with multiple sclerosis on insomnia symptoms and sleep quality: A systematic review of randomized controlled trials

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Abstract Patients with multiple sclerosis (MS) often experience reduced health-related quality of life and mental health comorbidity. The prevalence of insomnia disorder and sleep quality impairments in MS patients ranges from 47% to 62%. Nevertheless, these problems often remain underdiagnosed and undertreated. This review systematically and critically assesses evidence from randomized clinical trials which evaluated the efficacy of different clinical interventions targeting mental and general health in patients with MS on insomnia symptoms and sleep quality. Pubmed, PsycINFO and Medline databases were systematically searched. Eligible studies included adults $\geq$ 18 years with MS diagnosis; were randomized clinical trials; and reported pre and post-treatment data for primary or secondary outcomes. Nine studies were selected including 755 adults with an MS diagnosis. Studies evaluated the efficacy of various treatments: psychological interventions (5); pharmacotherapy, including medications for fatigue, cannabis extract and melatonin (3); energy conservation therapy (1). Preliminary support was found for psychological interventions and cannabis extract. This work highlights the important need for more high-quality randomized controlled trials for interventions targeting insomnia in MS patients.

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Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative inflammatory condition. Mental disorder comorbidity is thought to be underdiagnosed in people with MS (Marrie et al., 2009), although it is associated with diminished treatment adherence, increased somatic symptoms, and impairment of both functional ability and social functioning (Chwastiak & Ehde, 2007). Poor sleep and insomnia are prevalent health concerns and have been linked to several problems such as distress, depression and increased risk of other forms of psychopathology (Baglioni et al., 2011; Hertenstein et al., 2019). Among individuals with chronic illnesses, sleep dysfunction, such as insomnia symptoms that include difficulties initiating and maintaining sleep and impaired sleep quality, can potentially increase disease impact and reduce overall mental health, work productivity, and utilization of health care services (Manocchia, Keller & Ware, 2001). Insomnia disorder is characterized by disturbed nocturnal sleep (difficulty initiating and maintaining sleep > 30 minutes and early awakening) and related daytime impairment (fatigue, cognitive and mood impairment, sleepiness; American Association of Sleep Medicine, 2014). Clinical guidelines have indicated that a first-line treatment for insomnia disorder is Cognitive Behavioural Therapy for Insomnia (CBT-I). This treatment usually consists of techniques targeting sleep hygiene (health practices and environmental factors that may promote or disrupt sleep), relaxation training, stimulus control therapy (aiming to re-establish the association between bed and sleep); sleep restriction therapy (aiming to curtail the time in bed to the actual amount of sleep being achieved) and cognitive strategies (Riemann et al., 2017).

The prevalence of insomnia symptoms and poor sleep quality in individuals with MS ranges from 47% to 62% (Merlino et al., 2009), and these results are significantly higher compared to the general population rates of approximately 10% (Riemann et al., 2017). Poor sleep quality could harm patients' health and quality of life (increasing sleepiness, impairment of cognition, mood fluctuation) contributing even further to the overall disease burden (Amtmann, Bamer, Kim, Chung, Salem, 2018). Despite its negative impact, however, insomnia disorder remains underdiagnosed and undertreated in MS (Brass, Li, & Auerbach, 2014). Previous literature has suggested that treatment of insomnia disturbances could have a beneficial impact on the quality of life and functional status of patients with MS beyond simply improving night-time sleep (Braley & Chervin, 2015), and thus timely recognition and appropriate interventions are needed.

To date, no systematic summary of the efficacy of different clinical interventions targeting mental and general health on insomnia symptoms and sleep quality has been conducted in patients with MS. This issue is of considerable importance for guiding clinical and research guidelines, and therefore the present systematic review aims to systematically summarize and evaluate results from randomized clinical trials (RCT) of the efficacy and safety of different clinical interventions for improving insomnia symptoms, perceived sleep quality or insomnia severity in this population.

Method

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting systematic reviews and meta-analyses (Liberati et al., 2009; see Document S1 in Supplemental Material) and preregistered in the PROSPERO database, submission registration ID: CRD42020196695.

Study selection

Study eligibility was assessed using the Population, Intervention, Comparison, Outcomes and Study design (PICOS) approach (O'Connor, Green & Higgins, 2008). In order to be included, studies had to fulfil all following inclusion criteria: 1) Population: adults (≥18 years) with MS diagnosis; 2) Intervention: all types of clinical intervention (cognitive behavioural therapy, behavioural intervention, psychoeducation, pharmacological treatment, mindfulness, energy conservation, relaxation, etc.) targeting mental and general health; 3) Comparison group: all types of control groups (active or inactive); 4) Primary outcomes: insomnia symptoms (sleep onset latency; nocturnal wakefulness); perceived sleep quality and insomnia severity measured as primary or secondary outcomes; Secondary outcomes: fatigue; cognitive and mood impairment; sleepiness; quality of life; mental disorders, other sleep disturbances; 4) Study design: RCT; 5) Language: English, Italian, German, Spanish, French.

Search procedure

Databases ''Pubmed'', ''PsycINFO'' and ''Medline'' were systematically searched with no start time date until November 2020 according to the following keywords: ''(multiple sclerosis*[title/abstract]) and (insomnia*[title/abstract] or sleep*[title/abstract]) and (treat* [title/abstract] or therap*[title/abstract] or intervention [title/abstract])''. The first author and a graduate student conducted the literature search, screened titles and abstracts of potentially eligible studies, examined full-texts and extracted descriptive data. Whenever the inclusion or exclusion of a study was in doubt, it was discussed with the last author. The final selection of articles was discussed by all authors. Following this initial search, the search procedure was expanded through identifying further studies from the references of the screened full-texts. Finally, in order to collect data from non-published studies, the first author screened published conference proceedings from 2014 to 2019 published in the *Journal of Sleep Research* (conference proceedings from the biannual meeting of the European Sleep Research Society, ESRS). The searches and the screening were conducted on Citavi 6 software (https://www.citavi.com).

Data extraction

The first author extracted data and any doubts were discussed with all authors. For each selected study, sociodemographic, clinical and methodological variables were

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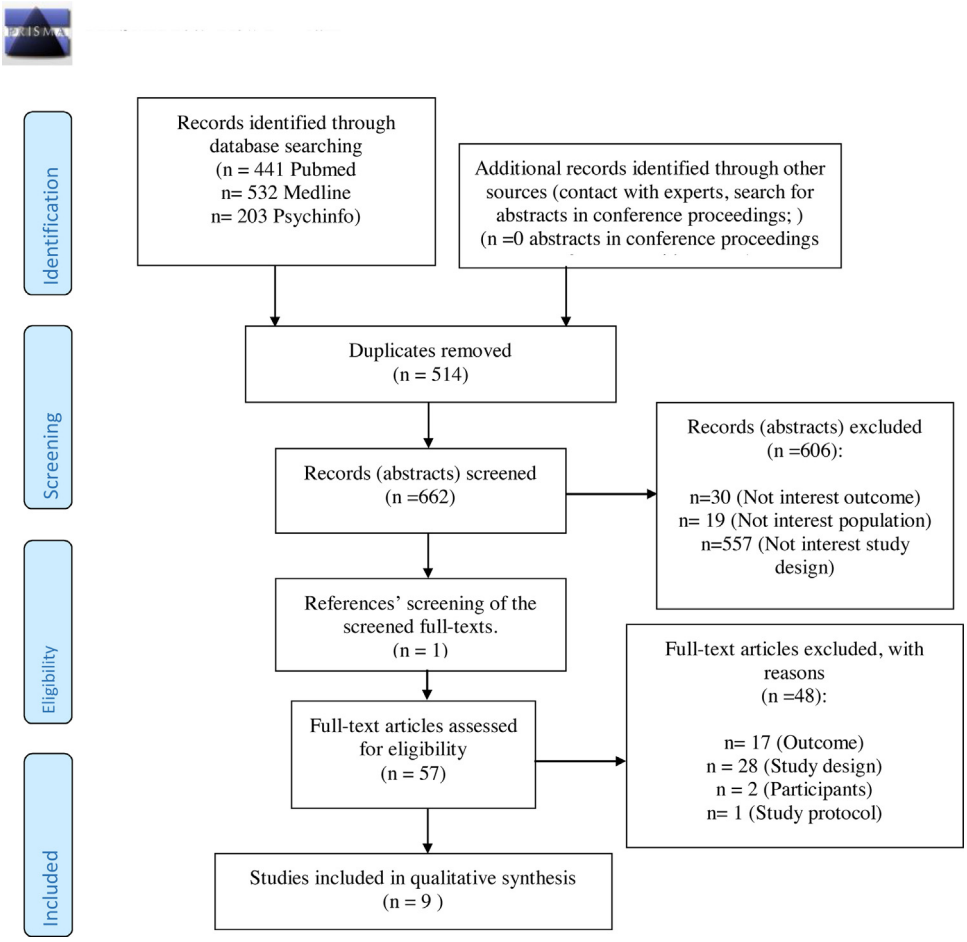

Figure 1 Search flow diagram.

PRISMA 2009 flow diagram.

recorded. When provided, data concerning the onset of multiple sclerosis and recurrence were extracted, as well as information concerning: sample size; country; mean age; type of sclerosis; onset; recurrence; study design; follow-ups; intervention; control; outcome of interest (primary and secondary outcomes as indicated in the inclusion criteria).

Risk of bias assessment

The revised Cochrane Collaboration's tool for assessing risk of bias (Sterne et al., 2019) was used. This tool assesses the following potential areas of bias: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result.

The tool includes algorithms that map responses onto a proposed risk-of-bias judgment for each domain. Following Cochrane guidelines, the possible risk-of-bias judgments are: ''Low risk of bias''; ''Some concerns''; ''High risk of bias''. Studies are judged to be at low risk of bias if they received ''low risk'' judgment for all domains. Studies are judged to raise some concerns if they received ''some concerns'' judgment in at least one domain but not at high risk of bias for any domain. Finally, studies are judged to be at high risk of bias if they received ''high risk'' judgment in at least one domain or if they received ''some concerns'' for multiple domains in a way that substantially lowers confidence in the result. The first and last authors rated each study through decision by consensus.

Results

Study selection

Fig. 1 illustrates the detailed flow chart of the selection process. Database searching yielded 1,176 abstracts. Of these, 514 were duplicates. After removing duplicates a total of 662 abstracts remained. Titles and abstracts were examined for relevance and 606 were excluded. Reference lists of the retrieved original articles were screened and 1 more record was found. Fifty-seven records were scrutinized and 48 studies were excluded for the following reasons: not a RCT ($n = 28$); not an outcome of interest ($n = 17$); not a sample of MS patients ($n = 2$); study protocol issues and no data available ($n = 1$). A total of 9 studies met the inclusion criteria and were therefore reviewed.

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Study characteristics and quality assessment

A summary of the included studies is reported in Table 1 (further information is summarized in supplemental material S2). RCTs tested the efficacy of the following different interventions: psychological interventions ($n = 5$); pharmacotherapy ($n = 3$) and energy conservation (i.e. analysing and modifying activity patterns to cope with fatigue, $n = 1$). The sample sizes ranged from a minimum of 23 to a maximum of 279 participants, for a total of 755 individuals (Female: 457, Male: 298, age range 36.9—54.8 years). Only one of the included studies reported data exclusively on women. Reported mean MS duration varied across studies from 24.8 months to 15.1 years. All studies used only self-reported measures to assess sleep parameters as outcomes. Only two of the included studies did not carry out a follow-up, while other studies included follow-ups ranging from 2 weeks to 6 months.

Detailed risk of bias assessment' evaluations are presented in Supplementary Material Document S3 including judgments and reasons based on Cochrane's criteria for each domain. Risk of bias assessment' scores are detailed in Fig. 2. Only one study received the judgment of ''high risk of bias'', dependent on ''Some concerns'' judgements in two areas: ''Randomization process'' and ''Selection of the reported results''. Two studies were categorized as a ''Some concerns judgment'' as both received ''Some concerns'' judgement in the ''Selection of the reported results'' area. Finally, five studies received a ''Low risk of bias'' final judgement.

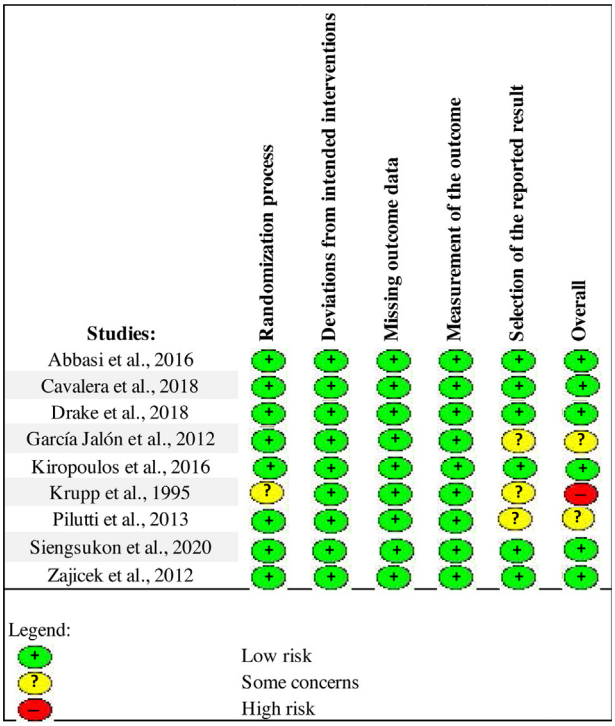

Figure 2 Evaluation of risk of bias of selected studies.

Efficacy of psychological interventions

In this systematic review, three studies tested the efficacy of CBT strategies on sleep quality and insomnia-related outcomes. In the first study (Abbasi, Alimohammadi & Pahlavanzadeh, 2016), authors evaluated the effect of a group CBT program targeting negative thoughts on sleep quality in 66 women with MS. The intervention was composed of eight weekly sessions and was designed to determine, challenge and change negative cognitions of the participants based on ABCD model (A: event or behaviour, B: belief, C: emotional and behavioural consequences and D: challenging and confronting the thoughts). The control group was treated as usual (TAU, medications for MS) and was composed of 33 women (average age 33.2 years) and with a mean MS duration of 6.1 years. The CBT intervention group was composed of 33 women (average age 35.3 years) and with a mean MS duration of 5.6 years. Results indicated significant improvement compared to pre-treatment of self-reported sleep quality after the intervention and at follow-up (after 3 months) in the CBT group compared to the control group ($F = 89.807$, $P < 0.001$).

Moreover, Kiropoulos et al. (2016) examined a CBT intervention targeting depressive symptoms, anxiety, fatigue and pain (as primary outcome) and quality of life, sleep difficulties, MS illness acceptance, active coping skills, social support and resilience (as secondary outcomes) in individuals who received an MS diagnosis within the last 5 years. The intervention was composed of progressive muscle relaxation, breathing exercises, activity scheduling, problem solving, cognitive exercises which helped individuals to identify, challenge and manage thoughts and beliefs. The control condition was TAU (usual medical care from their neurologist). The CBT group included 13 women, with a mean age of 34.6 years and duration of the disease was 26.2 months, and the TAU group included 9 women, aged on average 29.2 years and average duration of the disease 25.5 months. The authors found that at post-intervention the CBT intervention group reported significantly less self-reported depressive symptoms compared to the TAU group. Smaller effects were found for level of anxiety, fatigue and self-reported sleep quality ($F = 11.06$, $P < 0.001$).

One study (Siengsukon, Alshehri, Williams, Drerup and Lynch, 2020) evaluated the efficacy of Cognitive Behavioral Therapy for Insomnia (CBT-I). Particularly, the authors tested the efficacy of a CBT-I intervention composed of 6 weekly sessions on psychoeducation; sleep hygiene, mindfulness, relaxation; cognitive reappraisal and relapses prevention. They compared this intervention with active controls (involved in gentle stretching and self-selected light or sedentary activity) and a sleep education control group (receiving single-page handout concerning sleep promotion). Mean age of participants was 50.4 years for both CBT-I ($F = 9$, $M = 1$) and active control ($F = 8$; $M = 2$), and 56.9 years for the sleep education control group ($F = 10$, $M = 0$). Results showed a significant and positive improvement of all groups on insomnia severity and sleep quality, with the CBT-I group demonstrating the largest change (insomnia severity: $F = 2.729$; sleep quality: $F = 2.314$, $P < 0.001$) compared to the other two groups. Moreover, significant improvements in fatigue were found in the CBT-I group ($F = 1.064$, $P < 0.001$).

One study (Pilutti, Dlugonski, Sandroff, Klaren & Motl, 2014) assessed the efficacy of an internet-delivered behavioural intervention aimed at increasing physical

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Table 1 Characteristics of selected studies.

Author	Sample size	Country	Mean age (years)	Males/females	MS duration	Experimental intervention	Control intervention	Target of the intervention	Outcomes	Instruments
Abbasi et al., 2016	66	Iran	Intervention: 35.3; control: 33.2	All females	Intervention group: 5.6 (5.8) years; control group: 6.1 (6.5)	Cognitive behavioural therapy	Inactive control group	Sleep quality	Self-reported sleep quality	Pittsburgh Sleep Quality Index
Cavalera et al., 2019	121	Italy	Intervention: 42.2; control: 43.1	F: 78; M: 43	Intervention: 11.1; control: 12.2 years	Online mindfulness-based stress reduction	Online psychoedu-cation	Quality of life, psycho-logical well-being, sleep, and fatigue	Self-reported sleep problems	Medical Outcome Study Sleep
Drake et al., 2018	31	UK	54.8	F: 18; M: 13	n/a	Melatonin	Placebo	Nocturia	Self-reported sleep quality	Pittsburgh Sleep Quality Index
García Jalón et al., 2013	23	Ireland	Intervention: 45.8; control: 52	F: 16; M: 7	Intervention: 11; control: 14 years	Energy conserva-tion program	Peer support group	Fatigue	Sleepiness; self-reported sleep disturbance	Epworth Slepiness Scale
Kiropoulos et al., 2016	30	Australia	36.9	F: 22; M: 8	24.8 months	Cognitive behavioural therapy	Treatment as usual	Depressive symptoms	Self-reported sleep quality	Pittsburgh Sleep Quality Index
Krupp et al., 1995	93	USA	Intervention1: 40.2; inter-vention2: 40.7; placebo: 41.4	F: 66; M: 27	Intervention1: 124 months; intervention2: 136 months; placebo: 80 months	Pemoline; amantadine	Placebo	Fatigue	Self-reported sleep disturbance	St Mary's Hospital Sleep Questionnaire
Pilutti et al., 2014	82	USA	Intervention: 48.4; control: 49.5	F: 62; M: 20	Intervention: 10.6 years; control: 13 years	Behavioural therapy	Waiting list	Fatigue, depression, anxiety, pain, sleep quality, and quality of life	Self-reported sleep quality	Pittsburgh Sleep Quality Index
Siengsukon et al., 2020	30	USA	Intervention: 51.1; active control: 50.4; brief education control: 56.9	F: 27, M: 3	Intervention: 17.3 years; active control: 9.1 years; brief education control: 18.3 years	Cognitive behavioural, therapy for insomnia	Active control and one-time brief education control	Insomnia symptoms and sleep quality	Insomnia severity and self-reported sleep quality	Insomnia Severity Index and Pittsburgh Sleep Quality Index
Zajicek et al., 2012	279	UK	Intervention: 51.9; control: 52	F: 102; M: 177	Intervention: 14.5 years; control: 15.1 years	Cannabis extract	Placebo	Pain	Self-reported sleep quality	Category rating scale

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activity levels (web-based video coaching), compared to a waiting list group. Mean age of participants was 48.8 years for CBT group (F = 30, M = 11) and 49.5 years for the waiting list group (F = 32, M = 9), while mean duration of the disease was 10.6 years for CBT group and 13 years for the waiting list group. Results showed a significant and positive improvement of the CBT intervention on fatigue severity, depression and anxiety. Nevertheless, no significant improvements in self-reported sleep quality were found (F = 3.66, $P = 0.06$).

Finally, Cavalera et al. (2019) conducted a study that aimed to test the efficacy of a mindfulness-based intervention in individuals with MS on quality of life and stability of the results at a 6-month follow-up. Particularly, participants were randomly assigned to an online mindfulness-based intervention composed of a mindfulness component and music meditation, psychoeducation and acceptance (mean age of participants: 42 years; mean duration of the disease: 11 years, M = 18; F = 36) or to an active control group (online psychoeducation regarding stress management, relaxation training, sleep hygiene, fatigue, and social relationship; mean age of participants: 43 years; mean duration of the disease: 12 years; M = 25; F = 42). Participants were assessed three times: at recruitment, after 2 and 6 months after the interventions. Results showed a strong effect of the mindfulness program on self-reported sleep problems at the post-intervention evaluation (F [1,111] = 16.257, $P < 0.001$), but no statistical difference between groups was found after 6 months.

Efficacy of pharmacotherapy

In this systematic review, three studies were included that assessed the efficacy of pharmacotherapy on sleep-related parameters. The first study by Krupp and colleagues (1995) tested the efficacy of pharmacotherapy for fatigue. The second study by Zajicek et al. (2012) evaluated the efficacy of a cannabis extract on perceived sleep disturbances. The third study by Drake et al. (2018) evaluated the effect of melatonin on sleep quality.

Krupp et al. (1995) administered the following for 6 weeks to 93 MS patients with severe fatigue: pemoline (a Central Nervous System stimulant) in 18.75-mg tablets (mean age: 40.2 years; mean duration of the disease: 124 months, F = 19; M = 8), amantadine (antiviral agent, in 100-mg tablets, mean age: 40.7 years; mean duration of the disease: 136 months, F = 21; M = 10), or a placebo (mean age: 41.4 years; mean duration of the disease: 80 months, F = 26; M = 9). Results showed that the amantadine group had a significantly greater reduction in fatigue compared to other groups, but no significant changes were found in perceived sleep disturbance in the three groups.

Zajicek et al. (2012) randomized 143 patients to cannabis extract (mean age: 51.9 years, F = 88; M = 55) and 134 to a placebo group (mean age: 52 years, F = 87; M = 47). The study consisted of a pre-treatment screening period of 1/2 weeks, a 2-week dose titration phase and a 10-week maintenance phase. Participants were assessed at 2, 4, 8 and 12 weeks after the beginning of treatment. Results showed that self-reported sleep quality and complaints were improved in the cannabis extract group compared to placebo.

Finally, Drake et al. (2018) evaluated the effect of melatonin on self-reported sleep quality in MS patients with nocturia problems. Particularly, this was a randomized, double blind, placebo controlled crossover trial with two groups. Treatment consisted of 2 mg per night of capsulated sustained-release melatonin or a placebo capsule per night for 6 weeks each, separated by a washout period of 4 weeks. In total 13 men and 18 women (mean age 54.8 years) were randomized. No significant improvement was found in self-reported sleep quality.

Efficacy of energy conservation intervention

Energy conservation can be defined as education and promotion for people with multiple sclerosis on behavioural changes to use energy resources more effectively (how to analyse and modify their own activity patterns in order to cope with their fatigue). A study by Garcia Jalon et al. (2013) assessed the efficacy of energy conservation for fatigue management in MS patient (mean age 45 years, mean duration of the disease: 11 years, F = 10; M = 3) compared to a peer support control group (mean age 52 years, mean duration of the disease: 14 years, F = 6; M = 4). In this study, sleep complaints were evaluated as a secondary outcome. No significant improvement or differences between the two groups for sleep problems was reported.

Discussion

This is the first systematic review of RCTs on the efficacy of different types of clinical interventions targeting mental and general health in improving insomnia symptoms and sleep quality in MS patients. Nine RCT studies were included, involving different types of interventions. Table 2 summarizes the main results for each study, highlighting intervention type, study characteristics and assessed outcome.

Results from this systematic review highlight the fact that relatively few RCTs have been conducted to date. In addition, although the selected studies evaluated the efficacy of different clinical interventions for mental or general health on insomnia symptoms as outcomes, only one RCT was available testing an intervention directly targeting insomnia in patients with MS. Despite the fact that this study (Siengsukon et al., 2020) found CBT-I to be effective in improving insomnia symptoms, sleep quality and fatigue, small effects were reported and their sample was limited. Since the efficacy of CBT-I is well known both for insomnia and comorbid conditions (e.g. Riemann et al., 2017; Mitchell, Bisdounis, Ballesio, Omlin, & Kyle, 2019; Wu, Appleman, Salazar, & Ong, 2015), these preliminary results nonetheless set the stage for larger future investigations on the efficacy of structured and adapted CBT-I interventions in MS patients.

Furthermore, structured interventions based on CBT strategies directed at improving depressive symptoms, fatigue and negative thoughts were effective with different effect sizes for sleep quality in patients with MS. Nevertheless, an intervention based on behavioural strategies was not efficacious when focusing only on physical activity as the outcome. Furthermore, results for a mindfulness

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Table 2 Efficacy of different interventions on assessed sleep-related outcomes.

Intervention	Number of sessions (n =)	Sleep quality	Self-reported sleep disturbance
Psychological interventions			
Abbasi et al., 2016	8 weeks	✓	
Kiropoulos et al., 2016	8 weeks	✓	
Pilutti et al., 2014	6 months	✗	
Siengsukon et al., 2020	6 weeks	✓	✓
Cavalera et al., 2019	8 weeks		✓ , but not at follow-up
Pharmacotherapy			
Krupp et al., 1995	6 weeks		✗
Zajicek et al., 2012	12 weeks	✓	✓
Drake et al., 2018	6 weeks	✗	
Energy conservation intervention			
Garcia Jalon et al., 2012	5 weeks		✗

✓ : the intervention was efficacious in this outcome; ✗ : the intervention was not efficacious in this outcome.

intervention showed an improvement of self-reported sleep problems, but this was not maintained at follow-up. More focused trials on insomnia outcomes are needed to determine the effectiveness of CBT strategies in this population and to understand the mechanisms that could improve the health and quality of life of patients with MS complaining insomnia symptomatology.

Regarding the efficacy of pharmacotherapy for sleep quality in MS patients, our systematic review showed that only cannabis extract seemed to be effective in improving sleep quality but not pemoline, amantadine or melatonin. European and US guidelines have highlighted that pharmacological treatment for insomnia in general may have a short-time positive effect on sleep outcomes, which however are weak (American Academy of Sleep Medicine, Sateia, Buysse, Krystal, Neubauer, & Heald, 2017) and their long-term efficacy is unknown and could involve risks of side-effects (Baglioni et al., 2020). Similarly, the efficacy of melatonin for insomnia disorder is currently debated. Particularly, melatonin seems to be safe and effective in reducing sleep onset latency but with a small effect (Riemann et al., 2017). Previous studies that evaluated the effects of cannabis on insomnia showed mixed results, suggesting that further investigation of this treatment is needed (Babson, Sottile & Morabito, 2017). No significant results were found for the energy conservation program. This finding could be explained by the fact that this intervention was focused on fatigue symptoms and tested only on a very small sample.

Despite knowledge that the majority of MS patients may be at risk for insomnia disorder, these problems often go unrecognized and untreated in this population (Brass et al., 2014). This could be due to the tendency of mental disorder practitioners to consider insomnia as a secondary problem. Indeed, the classical psychiatric point of view traditionally considered insomnia and poor sleep as symptoms of other disturbances, specifically depression. For this reason, as a secondary symptom, the idea was that insomnia disorder would be improved through the successful treatment of the primary disorder. Nevertheless, previous literature showed that insomnia symptoms continue to persist after successful treatment of other comorbid disturbances (e.g. depression, Vargas & Perlis, 2020). The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* identified for the first time insomnia as an independent disturbance that requires specific treatment. Furthermore, insomnia often precedes the development of psychopathology and is recognized as a risk factor for several health problems (Baglioni et al., 2011; Hertenstein et al., 2019; Taylor, Lichstein, & Durrence, 2003). For these reasons, early diagnosis and treatment of insomnia is essential for the prevention of future negative mental health and physical consequences. It is also important to note that acute insomnia symptoms can lead to chronic insomnia when left untreated, and that no specific guidelines for the treatment of insomnia disorder in patients with MS are available.

In the present systematic review, the role of psychological interventions was highlighted for ameliorating insomnia symptoms and sleep quality in patients with MS. Nevertheless, interventions focusing only on behavioural components appear to not be efficacious compared to multi-targeted psychotherapies (e.g. intervention on depressive symptoms; focus on negative thoughts or CBT-I). Despite the fact that psychotherapy was associated with significant improvement

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in sleep quality and insomnia symptoms, all studies were based on limited samples, observed small effects and tested long-term efficacy of their interventions over short periods of follow-up. For these reasons, this systematic review underlined a lack of evidence-based interventions, thus limiting strong conclusion relative to their efficacy.

More effort should be dedicated to clinical research assessing the effectiveness of different interventions targeting insomnia directly in this important and high-risk population. Particularly, future RCTs should investigate long-term efficacy of CBT as a first-line treatment for insomnia in patients with MS. Future studies should recruit larger samples and test the efficacy of CBT-I not only for improving insomnia symptoms and sleep quality but also for increasing health-related quality of life and preventing depression symptoms. In our systematic review, only one included study (Siengsukon et al., 2020) used the Insomnia Severity Index (ISI, Bastien, Vallières & Morin, 2001) to evaluate insomnia symptoms before and after the intervention

This systematic review was limited by the heterogeneity of studies that prevented a comprehensive estimation of all effects through meta-analysis. Other limitations include the low number of studies overall and the fact that not all interventions specifically targeted sleep outcomes. While the literature suggests CBT-I is an effective therapy for insomnia in patients with comorbid health conditions, it is not possible at this point to confirm its value as a specific intervention targeting sleep complaints in patients with MS. There is a pressing need to improve our knowledge of effective interventions for insomnia symptoms and sleep quality in patients with this illness in order to advance current clinical practice. Following the Cochrane Collaboration guidelines, systematic reviews can demonstrate where knowledge is lacking and, consequently, guide future research to address neglected topics in research (Centre for Reviews and Dissemination CFRA, 2009).

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Contribution of authors

V.B., C.B., F.M., and C.B.: conceptualization; V.B., and C.B.: methodology; V.B., C.B., F.M., and C.B.: writing — original draft preparation; V.B., C.B., F.M., and C.B.: writing — review and editing; C.B., F.M., and C.B.: visualization and supervision.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/

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