Master Thesis

The Effectiveness of Interventions in Reducing Sleep Problems in Chronic Pain: a Systematic Review on Randomized Controlled Trials

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Abstract

Background. Sleep problems and chronic pain are major health issues worldwide and often co-occur. Sleep problems in chronic pain populations can decrease the quality of life of patients and worsen the severity of the condition. Recent research suggests that sleep problems are a strong predictor of pain, implicating that adequate treatment of sleep problems in chronic pain populations may be beneficial. The current systematic review aimed to assess the effectiveness of interventions in reducing sleep problems in chronic pain populations.

Method. A systematic research was conducted in the electronic databases PubMed, PsycINFO and Web of Science, from May 2019 to June 2019. For each database, sleep-, pain- and RCT-related keywords were used. Inclusion criteria were: randomized controlled trials, English-language, interventions for sleep problems in chronic pain, participants with chronic pain for at least three months and published in the last 10 years (2009 – 2019). Children (≤17) were excluded.

Results. Of the 688 articles identified, twenty met the inclusion criteria and were examined in detail. Twelve studies concerned behavioral therapeutic interventions, seven studies concerned pharmacological interventions and one study concerned an alternative medicine intervention. Of the behavioral therapeutic interventions, cognitive behavioral therapy for insomnia resulted in significant improvements in sleep problems, as well as in self-efficacy, catastrophic thoughts regarding pain, daily functioning and emotional distress (symptoms of depression). These findings were obtained after treatment and persisted up to 6- and 12-months. Of the pharmacological interventions, pregabalin, eszopiclone and very low doses of cyclobenzaprine were effective in reducing sleep problems, and these changes were accompanied by significant reductions in pain severity. However, these results were found after treatment and a follow-up was not conducted. In the alternative medicine intervention, no significant results were found.

Conclusions. Cognitive behavioral therapy for insomnia seems effective in reducing sleep problems in chronic pain, and also improves self-efficacy, catastrophic thoughts regarding pain, daily functioning and emotional distress, which is important for the health-related quality of life of patients. Cognitive behavioral therapy is, therefore, a promising treatment option for sleep problems in chronic pain. Medications are not recommended, given the lack of long-term effectiveness, serious adverse effects, and the risk of habituation and tolerance. In addition, medications do not address psychological factors, which is important because reducing pain levels in chronic pain conditions is difficult.

Keywords: sleep problems, chronic pain, randomized controlled trials

Table of Content

Introduction

Sleep problems and chronic pain are major, global health issues. Both are most common reported complaints by primary care patients (Jank, Gallee, Boeckle, Fiegl, & Pieh, 2017).

Sleep plays a crucial role in brain function and systemic physiology. Despite the importance of sleep, up to 45 million people in Europe experience sleep problems. In the Netherlands, 10% of adults sleep less than the recommended sleep duration (seven to nine hours) and 6 to 13% of adults with a sleep duration within the recommended hours of sleep, still report sleep problems (Leone et al., 2018). Poor sleep in adults can increase the risk of negative health and functional outcomes, resulting in higher socioeconomic costs due to healthcare utilization, sick leave and reduced productivity (Leone et al., 2018).

Chronic pain, on the other hand, can be defined as pain persisting three months or longer. In Europe, the prevalence rate of chronic pain in adults ranges from 12% to 30% (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006). Due to its high prevalence and disabling nature, chronic pain has a substantial negative effect on both patients and society (Jank et al., 2017). For example, patients with chronic pain report that their condition reduces their ability to exercise, walk, do household chores, and maintain an independent lifestyle (Breivik et al., 2006). Furthermore, chronic pain patients experience difficulties in attending social activities, having sexual relations, and maintaining relationships with family and friends (Breivik et al., 2006). Moreover, chronic pain is often associated with psychological disorders such as depression and anxiety (Pilowsky, Crettenden, & Townley, 1985; Palermo & Kiska, 2005; O'Brien et al., 2010; Roberts & Drummond, 2016), suicidal ideation and suicide attempts (Ratcliffe, Enns, Belik, & Sareen, 2008). Finally, chronic pain also has an enormous economic burden (Breivik et al., 2006). In Europe, healthcare utilization and economic costs due to sick leave and decreased productivity result in billions lost annually (Breivik et al., 2006).

There is growing evidence that sleep problems and chronic pain often co-occur. In multiple studies at least 50% of adults suffering from chronic pain report sleep problems (Smith, Perlis, Smith, Giles, & Carmody, 2000; Pilowsky et al., 1985), and in some studies sleep problems are even as high as 70-88% (Smith & Haythornthwaite, 2004; Morin, LeBlanc, Daley, Gregoire, & Merette, 2006; Jank et al., 2017). More specifically, adults in chronic pain populations report difficulties falling asleep, sleep fragmentation and poorer sleep duration (Karaman et al., 2014; Keilani, Crevenna, & Dorner, 2017). Chronic pain patients with sleep problems also experience a longer sleep onset latency, fewer hours of sleep, more awakenings during sleep and less restful sleep as compared to chronic pain patients without sleep problems (Smith et al., 2000; Tang, Wright, & Salkovskis, 2007). Sleep problems in medical conditions

such as chronic pain can decline the quality of life of patients and aggravate the severity of the condition.

The strong relationship between sleep problems and chronic pain has long been proven (Bruni et al., 1997). However, the direction of the interaction has been debated for a long time. Initially, the relationship was assumed to be bidirectional (Lewin & Dahl, 1999), but this finding was not supported by the comprehensive review of Smith and Haythornthwaite (2004). Smith and Haythornthwaite's (2004) review of longitudinal studies, published prior to 2005, found a reciprocal relationship between sleep problems and chronic pain, with pain interrupting sleep and sleep problems further magnifying pain. In an attempt to contribute to the field regarding the direction and mechanisms of the association between sleep and pain, Finan, Goodin and Smith (2013) further investigated prospective and experimental literature from 2005 to 2013. A main finding present in the population-based longitudinal studies considered by Finan et al. (2013) was that sleep problems predict new cases of chronic pain but also exacerbate existing chronic pain conditions. More specifically, sleep problems were found to heighten the risk of chronic pain in pain-free individuals, affect daily fluctuations in pain and worsen the long-term prognosis of chronic pain (Finan et al., 2013). At the same time, good sleep seemed to improve the long-term prognosis of chronic pain (Finan et al., 2013). Similarly, microlongitudinal studies support the finding that sleep problems are a stronger predictor of pain than vice versa. Furthermore, recent experimental studies suggest that sleep problems can impair important processes that play a role in the development and the continuation of chronic pain (Finan et al., 2013).

Even though it is unclear which mechanisms underlie the relationship between sleep and chronic pain, multiple factors have been found to contribute. For example, depression (Harman et al., 2002) and emotional responses to chronic pain (Tang et al., 2007) foster sleep disturbances in chronic pain patients. For the latter, health anxious chronic pain patients (as compared to non-health-anxious chronic pain patients) are more inclined to focus on bodily sensations, to detect heightened physical symptoms, have a lower pain tolerance and report more intense pain and greater anxiety (Harvey, Tang, & Browning, 2005), all of which in turn can interfere sleep (Tang et al., 2007). In addition, affective pain responses can also intensify sleep problems by activating the arousal system (Tang et al., 2007). Moreover, cognitive arousal – in particular, pain-related thoughts – before sleep may also contribute to sleep problems in people with chronic pain (Smith et al., 2000). Finally, it is possible that several coping behaviors, such as a decreased activity levels and frequent napping, can also increase sleep problems in chronic pain (Smith, Perlis, Carmody, Smith, & Gils, 2001).

In summary, recent findings demonstrate that adequate management of sleep problems may be an important objective in the treatment of chronic pain. Following the guidelines for general practitioners (Nederlands Huisartsen Genootschap, 2019), the first step in treating sleep problems is providing psychoeducation to correct incorrect assumptions regarding sleep and to increase insight into sleep-promoting and sleep-inhibiting activities. If sleep problems hold on, behavioral therapeutic treatments can be offered. Behavioral therapeutic treatments include stimulus control, sleep restriction, relaxation exercises, and cognitive therapy. Depending on the preferences and possibilities of the patient, the treatment can be supplemented with recommendations for structural exercise. Pharmacological treatments are recommended in exceptional cases only since evidence for long-term effectiveness is limited and adverse effects often remain. The exceptional cases in which pharmacological treatments can be considered are (1) short-term sleep problems due to acute, transient problems, if the suffering pressure becomes unacceptably high or (2) long-term sleep problems if no other improvement is possible and sleep problems result in impaired overall functioning.

Little is known if the aforementioned treatment options are also appropriate for sleep problems in those experiencing chronic pain or if these treatments reduce chronic pain as well. To date, few reviews have been published on sleep problems in chronic pain. These reviews, however, were focused on the neurobiological underpinnings (Christensen, Noel, & Mychasiuk, 2019) and psychological mechanisms in youth (Allen, Graef, Ehrentraut, Tynes, & Crabtree, 2016; Valrie, Bromerg, Palermo, & Schanberg, 2013). Specifically, the review of Christensen et al. (2013) focuses on neurobiological underpinnings and generates an overview of the sleep-pain relationship in adolescents by integrating existing literature on brain development, neurological changes in pain systems and the maturation of adolescent sleep-wake biology. The reviews of Valrie et al. (2013) and of Allen et al. (2016), on the other hand, focus on the relationship between sleep and pain in adolescents, including influential and moderator psychological factors. A review on the effectiveness of interventions on improving sleep in chronic pain populations has not been conducted but is nevertheless of great importance to treat and prevent the negative consequences of sleep problems in chronic pain. Therefore, the aim of the current systematic review is to address this gap in the literature by providing an overview of the effectiveness of interventions aimed to reduce sleep problems in chronic pain populations. The objectives of this research were as follows: 1) to examine characteristics of interventions aimed at improving sleep in patients with chronic pain and 2) to examine the effectiveness of interventions aimed at improving sleep in patients with chronic pain.

Method

Search strategy

By the aid of a librarian skilled, searches for studies were conducted in the electronic databases PubMed, PsycINFO and Web of Science, from May 2019 to June 2019. In each database, Randomized Controlled Trials (RCTs) were searched using sleep-, pain-, and RCT-related keywords. For the full search strategy for each database, see the Appendix.

Study Selection

The articles were selected following the guidelines of Higgins & Green (2011). In the first step, articles were identified through database searching. In the second step, duplicates were removed. In the third step, the titles and abstracts of articles were screened. In the fourth and final step, the full texts were screened against the specified inclusion and exclusion criteria. Inclusion criteria were: (1) Randomized Controlled Trials (RCTs), (2) English-language, (3) interventions for sleep problems in chronic pain, (4) participants with chronic pain for at least three months and (5) published in the last 10 years (2009 – 2019). Children (≤17) were excluded.

Quality Assessment

The risk of bias was assessed using the Cochrane Risk of Bias tool (Higgins & Green, 2011). Two independent reviewers (MA, LD) judged the risk of bias of the included studies. Subsequently, any differences in the assessment were discussed and a consensus was made. Finally, the supervisor of the study (GJP) assessed and approved the final proposal for the risk of bias assessment.

Results

Selection of Included Studies

The initial search in the databases PubMed, PsycINFO and Web of Science generated 688 records. Of these, 24 records were duplicates and were therefore removed. The remaining 635 records were screened according to titles and abstracts, resulting in the exclusion of 606 records that did not meet the exclusion criteria. Subsequently, the full texts of the remaining 29 records were assessed for eligibility. Of these, nine records were excluded because they were feasibility studies and therefore did not meet the exclusion criteria. The other 20 records were all included in the systematic review. These steps are visualized in the flowchart below (see Figure 1).

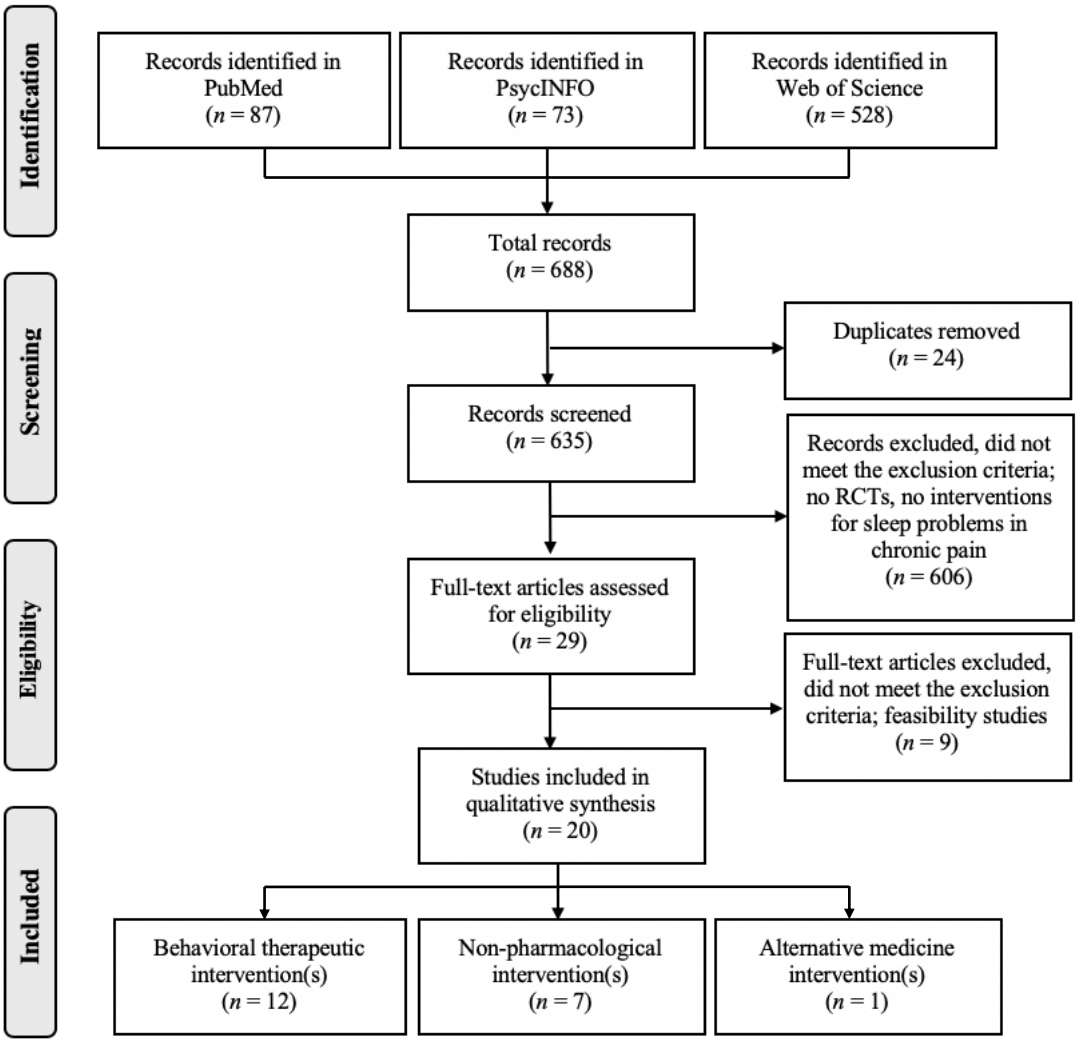

Figure 1. Flowchart literature search

Characteristics of the Included Studies

Characteristics of the included studies concerning population, inclusion criteria, recruitment, interventions, and moments of measurement are presented in Table 1. In the next sections, the included behavioral therapeutic interventions, pharmacological interventions, and alternative medicine intervention are respectively described in more detail.

Behavioral Therapeutic Interventions

Population characteristics. Of all (12) RCTs on behavioral therapeutic interventions, six were conducted in Europe (Sweden, Spain, Ireland and the United Kingdom) and six were conducted outside Europe (Israel and the United States of America). In six studies, the participants had met the diagnostic criteria of fibromyalgia (FM) and were recruited from a fibromyalgia clinic (Goldway et al., 2019; McCrae et al., 2019), a rheumatology service and pain unit (Lami et al. 2017; Martinez et al., 2013b; Miro et al., 2011; Sanchez et al., 2012) and from AGRAFIM (a FM association; Lami et al., 2017). In three studies (Jungquist et al., 2010; Pigeon et al., 2012; Tang, Goodchild, & Salkovskis, 2012) participants met the diagnostic criteria for non-malignant pain and were recruited from pain clinics. In two studies, the participants had met the diagnostic criteria of osteoarthritis pain defined by Grade II, III, or IV pain on the Graded Chronic Pain Scale (GCPS, McCurry et al., 2014; Vitiello et al., 2013) and were recruited from Group Health. In the remaining one study, the participants had chronic benign, neck, low back and/or generalized pain (Wiklund, Linton, Alföldi, & Gerdle, 2018) and were recruited through advertisements in local press and referrals from another study in the clinic. The samples of the behavioral therapeutic studies consisted of adults between 18 and 77 years old. In eight studies, the samples consisted of females and males (Goldway et al., 2019; Jungquist et al., 2010; McCrae et al., 2019; McCurry et al., 2014; Miro et al., 2011; Pigeon et al., 2012; Tang et al., 2012; Vitiello et al., 2013). However, females were in the majority in these studies. In three studies, the sample consisted mere of females (Sanchez et al., 2012; Martinez et al., 2013b; Lami et al., 2017), and in one study the gender of the participants was not explicitly indicated (Wiklund et al., 2018).

Intervention characteristics. ***Cognitive behavioral therapy (CBT)***. One study evaluated the effectiveness of Hybrid CBT (Tang et al., 2012), which consisted of CBT-I components combined with interventions to target cognitive-behavioral processes maintaining chronic pain. For four weeks, participants were individually offered weekly sessions. These sessions were dedicated to sleep psychoeducation, stimulus control therapy, sleep restriction

therapy, cognitive therapy, individual formulation, goal setting and behavioral activation, pain catastrophizing and safety-seeking behavior and mental defeat (Tang et al., 2012).

Four studies evaluated a CBT program for Insomnia (CBT-I) (Jungquist et al., 2010; Miro et al., 2011; Sanchez et al., 2012; Martinez et al., 2013b). One of these four studies (Jungquist et al., 2010) followed the treatment manual of Perlis, Jungquist, Smith, & Posner (2005). For eight weeks, participants were individually offered one session including four central components: sleep restriction therapy, stimulus control instructions, sleep hygiene instructions and cognitive therapy. The other three studies (Miro et al., 2011; Sanchez et al., 2012; Martinez et al., 2013b) followed the trial of Edinger et al. (2005). In these studies, participants received six weekly group sessions dedicated to psychoeducation, application of sleep restriction and stimulus control, physiological deactivation procedures, negative thoughts regarding insomnia and retaining achievements and preventing relapses. Compared to Sanchez et al. (2012), Martinez et al. (2013b) included a larger sample, subscales of the Pittsburg Sleep Quality Index (PSQI), self-report measures on fatigue, pain catastrophizing and self-efficacy for coping with pain and an assessment at follow-up (Martinez et al., 2013b).

Three studies compared cognitive behavioral therapy for pain and insomnia (CBT-PI), pain alone (CBT-P) and education only control (EOC) or usual medical care (UMC) (McCurry et al., 2014; Vitiello et al., 2013; Lami et al., 2017). Two of these studies (McCurry et al., 2014; Vitiello et al., 2013) followed the guidelines of the Lifestyles Study Protocol (Von Korff et al., 2012). CBT-P consisted of pain education, physical activation, goal setting, relaxation, activity pacing, guided imagery, and cognitive restructuring. CBT-PI consisted also of these elements but added sleep hygiene education, stimulus control, sleep restriction, and daily sleep monitoring. EOC included educational content regarding pain and management. The RCT of Vitiello et al. (2013) had a nine-month follow-up, while the RCT of McCurry et al. (2014) published results after 18 months. Furthermore, Lami et al. (2019) also evaluated CBT-PI and CBT-P but compared these two groups to an active control receiving UMC. The intervention consisted of nine weekly sessions. However, the protocol used in the trial of Lami et al. (2019) differed from the previous two studies. More specifically, in the trial of Lami et al. (2019), CBT-P was conducted according to the Fear-Avoidance Model of chronic pain (Leeuw et al., 2006; Vlaeyen & Linton, 2012) and aimed to change dysfunctional attitudes, emotional reactions and reinforcement contingencies that maintain pain behaviors. CBT-IP was conducted following the recommendations of the American Academy of Sleep Medicine and consisted of the aforementioned objectives and extended them to a sleep approach (Lami et al., 2019).

Exercise and acceptance and commitment-based stress management (ACT-bsm). One study measured the effectiveness of physical exercise and ACT-bsm on sleep disturbances in chronic pain (Wiklund et al., 2018). In the physical exercise group, the participants performed physical exercises in a group, twice a week for eight weeks. In the ACT-bsm group, the participants were offered a mixture of lectures and experience-based exercises. The content of the course was based on Acceptance and Commitment therapy at work and adapted into ACT-bsm to fit in the chronic pain setting (Wiklund et al., 2018).

Neurofeedback. One study measured the effectiveness of neurofeedback (Goldway et al., 2019). For five constructive weeks, participants received either real-neurofeedback or sham-neurofeedback.

Outcome measures. All 12 behavioral therapeutic studies assessed sleep, and 11 out of 12 studies assessed pain as well. For sleep, 23 different outcome measures were used, but the most frequently used were wake-after-sleep-onset, total sleep time, sleep efficiency, Insomnia Severity Index (ISI) and the Pittsburgh Sleep Quality Index (PSQI). For pain, 20 different measures were used, the most frequent being the Multidimensional Pain Questionnaire (MPQ), the Chronic Pain Self-Efficacy Scale (CPSS), the Pain Catastrophizing Scale (PCS) and the Pain Disability Inventory (PDI). Due to heterogeneity in outcome measures, the pooling of results was considered inappropriate. Therefore, results are described qualitatively in the next section.

Effectiveness of the interventions. ***Effectiveness of interventions at posttreatment and follow-up.*** Two trials were effective in improving sleep and pain outcomes after treatment and at a follow-up. First**,** in the trial of Martinez et al. (2013b), CBT-I had a greater improvement in sleep quality and chronic pain related self-efficacy as compared to sleep hygiene, both after treatment and at follow-up. Second, in the trial of Wiklund et al. (2018) a significant improvement in the exercise group was observed in insomnia severity and daily pain after treatment, and at a six- and 12-month follow-up.

Moreover, in the trial of Goldway et al. (2018), significant improvements were found after treatment and at follow-up in sleep quality for subjects receiving real-neurofeedback, while these results were not obtained for subjects receiving sham-neurofeedback. Furthermore, McCrae et al. (2019) found a statistically significant improvement after treatment and at follow-up in wake-after-sleep onset, sleep efficiency and sleep quality rating for subjects receiving CBT-I and CBT-P.

In the trial of Lami et al. (2018), significant results were obtained after treatment and at follow-up in pain catastrophizing and pain acceptance in subjects receiving CBT-P. It has to be

noted, however, that this trend inverted slightly at follow-up although there still was a significant difference compared to posttreatment (Lami et al., 2017).

Effectiveness of interventions at posttreatment only. In the trial of Jungquist et al. (2013) and Tang et al. (2012), significant results were obtained in sleep and pain outcomes after treatment, but these trials did not include a follow-up. In the trial of Martinez et al. (2013b), as compared to sleep hygiene, CBT-I resulted in significantly greater improvements in pain catastrophizing at posttreatment.

In the trials of Sanchez et al. (2012), Miro et al. (2011) and Pigeon et al. (2012), significant improvements were found at posttreatment in sleep outcomes. It has to be noted, though, that the trial of Sanchez et al. (2012) did not measure pain outcomes and that the trial of McCrae et al. (2019) and Miro et al. (2011) did not include a follow-up.

Effectiveness of interventions at follow-up only. In the trial of Goldway et al. (2019) significant effects were obtained in pain outcomes at follow-up. More specifically, Goldway et al. (2019) found a significant delayed improvement in pain intensity at follow-up in the real-neurofeedback group but not in the sham-neurofeedback group.

Pharmacological Interventions

Population characteristics. All (seven) RCTs on pharmacological interventions were conducted outside Europe (the United States of America, Canada, and Iran). In five studies, the participants had met the diagnostic criteria for fibromyalgia and were recruited via sites (Moldofsky, Harris, Archambault, Kwong, & Lederman, 2011; Moldofsky, Inhaber, Guinta, & Alvarez-Horine, 2010; Ware, Fitzcharlez, Joseph, & Shir, 2010; Roth, Lankford, Bhadra, Whalen, & Resnick, 2012) or participants' data were collected from two clinical trials (Russell et al., 2009). In two studies, participants had met the diagnostic criteria for chronic low back pain and were recruited through newspaper advertisements, posted announcements and physician referrals (Goforth et al., 2014) or via sites (Yarlas et al., 2016). The samples consisted of females and males between 18 and 77 years old, but females were in the majority in all samples.

Intervention characteristics. Seven studies measured the effectiveness of pharmacological treatment for sleep problems in chronic pain conditions. Of these, two studies measured the effect of pregabalin, while the other studies measured eszopiclone (Goforth, 2014), very low dose cyclobenzaprine (Moldofsky et al., 2011), sodium oxybate (Moldofsky et al., 2010), nabilone and amitriptyline (Ware et al., 2010) or buprenorphine transdermal system (Yarlas et al., 2016).

Outcome measures. All seven pharmacological studies assessed sleep, with four out of seven assessing pain as well. For sleep, 33 different outcomes were assessed, but the most frequent of which were total sleep time and sleep efficiency. For pain, six different measures were used. None of the four studies, however, used the same outcome measures. Due to heterogeneity in outcome measures, the pooling of results was considered inappropriate. Therefore, results are described qualitatively in the next section.

Effectiveness of the interventions. For the pharmacological interventions, effects were assessed after treatment but not at follow-up.

Effectiveness of interventions at posttreatment. First, some studies have found significant results in sleep and pain after treatment. In the trail of Roth et al. (2012), as compared to placebo, pregabalin revealed significantly greater in improvements in wake-after-sleep onset, total sleep time, latency to persistent sleep, sleep efficiency, number of awakenings after sleep onset, slow-wave sleep (stage 3 and stage 4 sleep), wake time during sleep, wake time after sleep and daily pain. In the trial of Goforth et al. (2014), as compared to placebo, eszopiclone resulted in significantly greater improvement in total sleep time, sleep onset latency, wake time after sleep onset, sleep efficiency, number of awakenings, quality of sleep, insomnia severity and pain ratings. In the trial of Moldofsky et al. (2011), very low doses of cyclobenzaprine resulted in a significant improvement in total time awake, total sleep time, sleep efficiency and pain, while these results were not found for subjects in the placebo group. Compared to placebo, subjects in the very low dose cyclobenzaprine group also had a significantly greater increase in Stage 2 sleep and a decrease in Stage 4 and REM sleep.

Second, some studies have found significant results after treatment in sleep outcomes but not in pain outcomes. In the trial of Yarlas et al. (2016), buprenorphine transdermal system (BTDS) 10/20 mcg/hour resulted in statistically significant higher overall sleep quality and less sleep disturbance, as compared to placebo. Likewise, subjects receiving BTDS 20 mcg/hour had statistically significant higher overall sleep quality and less sleep disturbance than subjects receiving BTDS 5 mcg/hour. In the trial of Russell et al. (2009), relative to placebo, therapeutic doses of pregabalin revealed statistically significant improvements in sleep quality, sleep disturbance, sleep quantity, sleep adequacy and sleep problems. The trial of Moldofsky et al. (2010) found that sodium oxybate (SXB) 6 mg/day resulted in greater improvement in wake-after-sleep onset, non-REM stage-2 sleep, slow-wave sleep, total non-REM sleep and phase A2/A3 CAP rate than placebo. SXB 4.5 mg/day only showed greater improvement compared with placebo in non-REM sleep. In the trial of Ware et al. (2010), nabilone was significantly

superior to amitriptyline in improving insomnia severity and no significant outcomes were found on the other outcome measures.

Non-pharmacological Intervention

One RCT examined the effectiveness of an alternative medicine intervention conducted in Europe, England. In this study, participants were males and females, but females were in the majority. Participants had all met the diagnostic criteria of migraine without aura (MWA) (Vagharseyyedin, Salmabadi, Taghanaki, & Riyasi 2019) and were recruited from the neurology clinic of a hospital. During the intervention, participants were allocated to either acupressure or sham acupressure. For four consecutive weeks, three times a week (before bedtime), the participants in the acupressure group were trained to apply acupressure on acupoints, while the participants in the sham-acupressure were trained to apply sham points. Results obtained no significant difference after treatment in and between both groups, and follow-up effects were not obtained.

Quality of the Included Studies

Table 7 provides an overview of the quality assessment. All included studies required the criteria for selection bias (e.g., random sequence allocation and allocation concealment), attrition bias (i.e., incomplete outcome data) and reporting bias (i.e., selective reporting). The criterium for blinding of participants was met in twelve studies but remained unclear in five studies and was not met in three studies. Moreover, the criterium for blinding of personnel was met in ten studies, remained unclear in seven studies and was not met in three studies. Furthermore, the criterium for detection bias was met in ten studies, remained unclear in eight studies and was not met in two studies. Finally, for all included studies, the risk for other bias remained unclear since all studies had limitations and it was difficult to estimate to what extent these limitations affect other forms of bias.

Table 1
Characteristics of Behavioral Therapeutic Interventions

First author, year of publication	Population, place, country	Inclusion criteria	Recruitment	Interventions (*n*)	Components and duration	With/without guidance	Moments of measurement
Goldway, 2019	Adults with fibromyalgia, Israel	Fibromyalgia****	Fibromyalgia clinic of the Institute of Rheumatology and from the Institute of Pain Medicine at Tel Aviv Medical Center in Israel	1. Real-NF 2. Sham-NF	10 components 5 weeks	Without	Pre-test, posttest, follow-up
Jungquist, 2010	Adults with insomnia comorbid with chronic pain, New York, USA	Chronic (>6 months) non-malignant pain; insomnia (>30 min sleep latency and/or minutes awake after sleep onset >3 days/week >6 months; preferred sleep phase between 10 pm and 8 am to avoid sleep phase disorders and shift workers; AHI <10; no other intrinsic sleep disorders; stable therapy for pain; no therapy prescribed specifically for insomnia; stable pain medication regime	From the community and local pain treatment clinics	1. CBT-I (19) 2. Control-subjects (9)	8 components 8 weeks	Without	Pre-test, post-test
Lami, 2018	Adults with FM and insomnia, Granada, Spain	Being a woman; age between 25 and 65; Fibromyalgia**** > 6 months; stable as regard to the intake of analgesics, antidepressants, or other drugs (sleep and pain) ≥ 1 month before the study; no other psychological treatment; insomnia**	Rheumatology Service and Pain Unit of Virgen de las Nieves University Hospital and from AGRAFIM (a FM association)	1. CBT-P (34) 2. CBT-IP (38) 3. UMC (41)	9 components 9 weeks,	Without	Pre-test, post-test, follow-up after three months
Martinez, 2013b	Females with fibromyalgia and insomnia, Granada, Spain	Being a woman; age between 25 and 60; fibromyalgia* >6 months; stable as regards the intake of analgesics, antidepressants or other drugs ≥ 1 month before the study; insomnia**	Rheumatology Service and Pain Unit of Virgen de las Nieves University Hospital in Granada, Spain	1. CBT-I (30) 2. SH (29)	6 components 6 weeks	Without	Pre-test, post-test, 3- and 6-month follow-up
McCrae, 2019	Adults with comorbid fibromyalgia and insomnia, Florida, USA	Being 18 years or older; willing to undergo randomization; able to read and understand English; pain > 6 months; confirmation of FM by tender point testing, using guidelines established by the American College of Rheumatology; insomnia complaints (sleep onset or awake time during night >30 min) > three nights per week for >6 months; sleep diary confirmation of insomnia (sleep onset or awake time during night >30 min) ≥ six nights during the 2 week baseline period; daytime dysfunction due to insomnia (mood, cognitive, social, or occupational impairment); no prescribed or over-the-counter sleep medications ≥ 1 month or stabilized on sleep medication for ≥6 months.	Rheumatology and sleep clinics at the University of Florida and through community advertisements.	1. CBT-I (39) 2. CBT-P (37) 3. WLC (37)	8 components, 8 weeks	Without	Pre-test, post-test, 6-month follow-up
McCurry, 2014	Adults with osteoarthritis pain and insomnia symptoms, USA	Significant arthritis pain defined by Grade II, III, or IV pain on the Graded Chronic Pain Scale (GCPS); significant insomnia defined by self-reported sleep difficulties ≥ 3 nights per week	Members of Group Health age 60 y or older who had received health care for OA in the prior 3 y were	1. CBT-P (122) 2. CBT-PI (122) 3. EOC (123)	6 components 6 weeks	Without	Pre-test, post-test, 9- and 18-month follow-up

		during the past month with at least one daytime sleep related problem, consistent with established research diagnostic criteria	screened for chronic pain and insomnia severity via mailed survey				
Miro, 2011	Women with comorbid chronic pain and insomnia, Granada, Spain	All patients met the diagnostic criteria for FM* and the criteria for insomnia**	Rheumatology Service and Pain Unit of Virgen de las Nieves Hospital in Granada, Spain	1. CBT-I (16) 2. SH (15)	6 components 5 weeks	Without	Pre-test, post-test
Pigeon, 2012	Adults with co-occurring chronic pain and insomnia, New York, USA	Chronic (≥6 months) non-malignant pain; insomnia (≥ 30 min sleep latency and/or minutes awake after sleep onset for > 3 days/wk for ≥6 months reported to originate after, and/or aggravated by the pain condition); preferred sleep phase between 10 pm and 8 am; apneae-hypopnea index<10	From the community through newspaper advertisements, and from local pain clinics via recruitment flyers	1. CBT-P (5) 2. CBT-I (6) 3. CBT-P/I (6) 4. WLC (4)	10 components 10 weeks	Without	Pre-test, post-test
Sanchez, 2012	Women with insomnia and fibromyalgia, Spain	Age between 25 and 60 years old; FM*; chronic insomnia**	From the Rheumatology Service and Pain Unit of the Hospital Universitario Virgen de las Nieves in Granada, Spain	1. CBT-I (13) 2. SH (13)	6 components 5 weeks	Without	Pre-test, post-test
Tang, 2012	Adults with chronic pain, UK	Chronic non-malignant pain of at least moderate severity (≥ 4 on the BPI) and for at least 6 months; clinical insomnia (≥15 on ISI); meeting duration (≥ 1 month), frequency (≥ 3 nights/week) and severity (sleep onset latency ≥30 min; wake after sleep onset ≥30 min; significant interference) criteria for insomnia	From a hospital pain clinic	1. Hybrid CBT (10) 2. Symptom Monitoring (10)	4 components 4 weeks	With, readings/ behavioral exercises between sessions	Pre-test, post-test
Vitiello, 2013	Adults with comorbid insomnia and osteoarthritis pain, Washington, USA	Clinically significant pain and insomnia; significant arthritis pain defined as Grade II, III, or IV pain on the Graded Chronic Pain Scale; significant insomnia was defined as meeting research diagnostic criteria for insomnia based on self-reported sleep difficulties (trouble falling asleep, difficulty staying asleep, waking up too early, or waking up unrefreshed), 3 or more nights per week during the past month with at least one daytime sleep-related problem.	Paid volunteers. Members of Group Health, an integrated health maintenance organization in western Washington state, who had received health care for OA at Group Health in the prior 3 years were screened for chronic pain and insomnia severity in a mailed survey	1. CBT-P (122) 2. CBT-PI (122) 3. EOC (123)	6 components 6 weeks	Without	Pre-test, post-test, 9-moths follow up

Wiklund, 2018	Adults with chronic pain, Linköping, Sweden	Chronic (> 3 months) benign neck, low back, and/or generalized pain	Linköping University Hospital (Linköping, Sweden); advertisements in local press, candidates applied through mail or phone; referred from another study in the clinic	1. ACT-bsm (99) 2. Exercise (100) 3. Active CON, discussing themes related to persistent pain (100)	7 components 7 weeks 16 components 8 weeks	Without	Pre-test, post-test, 6- and 12-moth follow-up

Notes. ACT-bsm = Acceptance- and Commitment-Based Stress Management; FM = Fibromyalgia; CBT = Cognitive Behavioral Therapy; CBT-I = Cognitive Behavioral Therapy for Insomnia; CBT-P = Cognitive Behavioral Therapy for Pain; CBT-PI = Cognitive Behavioral Therapy for Pain and Insomnia; CON = control; WP = Walking Program; SEC = Supervised Exercise Class; UMC = Usual Medical Care; UP = Usual Physiotherapy; BPI = Brief Pain Inventory; ISI = Insomnia Severity Index; SH = Sleep Hygiene; Real-NF = Real-neurofeedback; Sham-NF = Sham-neurofeedback; WLC = Wait-list Control; EOC = Education Only Control.

* having met the diagnostic criteria for FM (ACR; Wolfe et al. 1990)

** (DSM-IV-TR; American Psychiatric Association, APA, 2000)

**** met the American College of Rheumatology (ACR) 2001 criteria for FM

**** according to the American College of Rheumatology (ACR) 2010 criteria (Wolfe et al., 2011)

Table 2
Characteristics of Included Pharmacological Studies

First author, year of publication	Population, place, country	Inclusion criteria	Recruitment	Intervention, program, and duration	Section and duration	With/without guidance	Moments of measurement
Goforth, 2014	Adults with LBP, USA	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision diagnosis of insomnia because of a general medical condition (LBP); insomnia did not predate LBP onset by more than 1 mo; based on a sleep history taken by the study psychiatrist, the subject had a usual nightly TST less than 6.5 h and/or usual SOL more than 30 min for the month prior to screening; ISI greater than14 (at least moderate insomnia); were 21–64 y of age; VAS pain greater than 40; PGI Pain greater than 2 (at least moderate severity); more back pain than leg pain; no signs of spinal nerve root compression; normal motor strength on physical exam; LBP duration longer than 3 mo; pain inferior to T12 and superior to the gluteal fold	Newspaper advertisements, posted announcements, and physician referrals	1. Eszopiclone (ESZ) plus naproxen (32) 2. Placebo (PBO) plus naproxen (20)	4 weeks	Without	Prenaprosyn baseline, postnaprosyn baseline, week 1, week 2, week 4
Moldofsky, 2011	Adults with FM and disrupted sleep, Canada	Male and female patients; 18 to 65 years of age; FM*** and sleep disturbance; nonrestful sleep, more nights than not for at least 3 months before the start of double-blind treatment; a-nonREM EEG sleep anomaly at screening; signed informed consent	Two Canadian websites	1. VLD CBP (18) 2. Placebo (18)	8 weeks	Without	Pre-test, post-test
Moldofsky, 2010	Adults with FM, Toronto, Canada	PVAS > 4 on a 0 to 10-point VAS, based on patient diary records for the week prior to randomization; discontinue opiates, antidepressants, cyclobenzaprine, and tramadol; continue with any preexisting nonpharmacologic regimen; restrict rescue analgesic therapies to the use of acetaminophen ≤ 4000 mg/day, ibuprofen ≤ 1200 mg/day, naproxen ≤ 660 mg/day, or ketoprofen ≤ 75 mg/day; forego ingestion of alcohol; and for women who were not surgically sterile or postmenopausal ≥ 2 years, use a medically accepted method of birth control	Twenty-one clinical sites in the continental US	1. Sodium Oxybate 4.5 (51) 2. Sodium Oxybate 6g (46) 3. Placebo (54)	8 sections, 8 weeks	Without	Pre-test, post-test, and in-between
Roth, 2012	Adults with comorbid fibromyalgia and sleep disturbances, USA	Male or female patients; ages ≥18 years; diagnosed with FM**; a history of disturbed sleep on the screening interview, reflected by difficulty in maintaining sleep for ≥3 nights/ week for ≥1 month prior to screening interview; maintaining a normal daytime/awake nighttime/asleep schedule (bedtime between 9:00 PM and midnight), with 6.5–8.5 hours in bed each night and ≥3 hours of variation in the night-to-night bedtime; subjective	Nineteen sites across the US, Canada, and Germany	1. Pregabalin > placebo sequence (59) 2. Placebo Pregabalin sequence (60)	4 weeks	Without	Pre-test, post-test

		sleep entry criteria, recorded during screening and prior to randomization via an interactive voice recognition system (IVRS) for a minimum of 5 daily IVRS diary data points after visit 2, were subjective TST ≥6 hours and subjective WASO ≥60 minutes for ≥3 nights/week during the screening period. PSG entry criteria (conducted on 2 consecutive nights at visit 3) included the average of 2 PSG nights of WASO¬45 minutes and TST of 3.0–6.5 hours.					
Russell, 2009	Adults with FM and sleep disturbance symptoms, New York, USA	≥18 years of age; FM defined by ACR-criteria; an average daily diary pain score of ≥ 4 on NRS; a score of at least 40 mm on the 100 mm VAS of the Short- Form McGill Pain Questionnaire.	Data were collected from two clinical trials evaluating pregabalin for the management of FM in the United States	1. Pregabalin (300mg/day, 450mg/day, 600mg/day) (n) 2. Pregabalin placebo (n)	12 weeks	Without	Pre-test, post-test
Ware, 2010	Men and non-pregnant women (≥18) with FM and chronic insomnia, Canada	FM; self-reported chronic insomnia (defined as disturbed sleep either every night or every other night for the past 6 months)	Pain Clinic of the McGill University Health Centre	1. Nabilone (0.5–1.0 mg before bedtime) (29) 2. Amitriptyline (10–20 mg before bedtime) (29) 3. Active control (29)	5 sections, 10 weeks	Without	Each period was of 2-wk duration separated by a 2-wk washout phase. The total study period was for 10-wk, including initial and final 2-wk washout periods.
Yarlas, 2016	Sleep outcomes in adults with moderate-to-severe CLBP, USA	Moderate to severe chronic low back pain	75 study sites throughout the United States	1. BTDS 10/20 mcg/hour vs placebo control 2. BTDS 20mcg/hour vs active control (BTDS 5mg/hour)	12 weeks	Without	Screening, run-in, week 4, week 8, week 12

Notes. BTDS = Buprenorphine transdermal delivery system; CLBP = Chronic Low Back Pain; ISI = Insomnia Severity Index; FM = Fibromyalgia; LBP = Low Back Pain; NRS = Numeric Rating Scale; PGI = Patient Global Impression; PSG = Polysomnography; SOL = Sleep Onset Latency; TST = Total Sleep Time; VAS = Visual Analogue Scale; WASO = Wake After Sleep Onset.

Table 3
Characteristics of Included Alternative Medicine Studies

First author, year of publication	Population, place, country	Inclusion criteria	Recruitment	Intervention, program, and duration	Section and duration	With/without guidance	Moments of measurement
Vagharseyyedin, 2019	Adults with migraine without aura, Iran	Diagnosis of migraine without aura (MWA) in accordance with the beta version of the 3rd edition of the International Classification of Headache Disorders (ICHD-3 beta) criteria; initial onset of migraine at least one year before the study; age of 18–60 years; basic literacy skills; a score of more than 5 for the Pittsburg Sleep Quality Index; no skin lesions (such as rash or wound) at acupoints; no drug addiction; and no affliction by serious mental disorders and chronic illnesses	Conveniently selected from the neurology clinic of Valiasr (PBUH) teaching hospital, which is affiliated to Birjand University of Medical Sciences (BUMS)	1. Acupressure (38) 2. Sham acupressure (38)	4 sections, 4 weeks	With (telephone contacts)	Pre-test, post-test

Table 4
Outcomes Behavioral Therapeutic Interventions

First author, year	Measures	Results*
		a. Post-treatment b. Follow-up
Jungquist, 2013	**Sleep (continuity and quality)**	
	Sleep Latency (SL)	a. CBT-I > Control $p = <.05$ b. –
	Wake after sleep onset (WASO)	a. CBT-I > Control $p = <.05$ b. –
	Number of awakenings (NAWK)	a. CBT-I > Control $p = <.05$ b. –
	Early Morning Awakenings (EMA)	a. NS b. –
	Total Sleep Time (TST)	a. NS b. –
	Sleep Efficiency (SE)	a. CBT-I > Control $p = <.05$ b. –
	Insomnia Severity Index (ISI)	a. CBT-I > Control $p = <.05$ b. –
	Pain	
	Multidimensional Pain Inventory (MPI) Pain Severity Scale	a. NS ($p = .2645$) b. –
	Multidimensional Pain Inventory (MPI) Pain Interference Scale	a. CBT-I > Control $p = <.05$ b. –
	Pain Disability Index (PDI)	a. NS ($p = .0656$) b. –
	Sleep diary measure, average daily pain	a. NS ($p = 0.6669$) b. –
	Biopsychosocial	
	Beck Depression Inventory (BDI)	a. NS ($p = .0318$) b. –
Lami, 2018	**Sleep**	
	Total-Sleep Quality (PSQI)	a. CBT-IP$^+$ $p = <.01$ b. NS
	Subjective Sleep Quality (PSQI)	a. CBT-IP$^+$ $p = <.05$ b. NS
	Sleep Latency (PSQI)	a. CBT-IP$^+$ $p = <.01$ b. NS
	Sleep Duration (PSQI)	a. NS b. NS
	Sleep Efficiency (PSQI)	a. CBT-IP$^+$ $p = <.05$ b. NS
	Sleep Disturbances (PSQI)	a. NS b. UMC > CBT-P $p = <.01$
	Pain	
	McGill Pain Questionnaire- Short Form (MPQ-SF)	a. NS b. CBT-IP$^+$ $p = <.05$
	Chronic Pain Self-Efficacy Scale (CPSS)	a. CBT-P$^+$ $p = <.001$ a. CBT-IP$^+$ $p = <.05$ b. NS
	Pain Catastrophizing Scale (PCS)	a. CBT-P$^+$ $p = <.001$ b. CBT-P$^-$ $p = <.05$
	Chronic Pain Acceptance Questionnaire (CPAQ)	a. CBT-P$^+$ $p = <.001$ b. CBT-P$^+$ $p = <.05$

	Fatigue		
	Multidimensional Fatigue Inventory, General fatigue (MFI)	a. 	UMC > CBT-P and CBT-IP p = <.001
		b.	NS
	Mood		
	Symptoms Check List 90-Revised (SCL-90-R), Anxiety scale	a.	NS
		b.	NS
	Symptoms Check List 90-Revised (SCL-90-R), Depression scale	a. 	UMC > CBT-P p = <.05
		b. 	UMC > CBT-P p = <.01
		b. 	UMC > CBT-IP p = <.01
	Impaired functioning		
	Fibromyalgia Impact Questionnaire (FIQ)	a. 	CBT-P+ p = <.05
		a. 	CBT-IP+ p = <.001
		b.	NS
Martinez, 2013b	**Sleep**		
	Pittsburgh Sleep Quality Index (PSQI) – Sleep quality total	a. 	CBT-I+ p = <.001
		a. 	CBT-I > SH p = <.05
		b. 	CBT-I > SH (1st follow-up) p = <.05
	Pain		
	McGill Pain Questionnaire- Short Form (MPQ-SF)	a. 	CBT-I > SH p = <.01
		b.	NS
	Chronic Pain Self-Efficacy Scale (CPSS)	a. 	CBT-I > SH p = <.05
		b. 	CBT-I > SH (1st and 2nd follow-up) p = <.05
	Pain Catastrophizing Scale (PCS)	a. 	CBT-I+ p = <.001
		a. 	CBT > SH p = <.05
		b.	NS
	Fatigue		
	Multidimensional Fatigue Inventory (MFI)	a. 	CBT-I+ p = <.05
		a. 	CBT-I > SH p = <.05
		b.	NS
	Mood		
	Symptoms Check List 90-Revised (SCL-90-R), Anxiety scale	a. b.	CBT-I+, p = <.05 NS
	Symptoms Check List 90-Revised (SCL-90-R), Depression scale	a. a. b.	CBT-I+, p = <.01 CBT-I > SH, p = <.01 CBT-I > SH, p = <.05 (1st follow-up)
	Impaired functioning		
	Fibromyalgia Impact Questionnaire (FIQ)	a. 	CBT-I+ p = <.05
		a. 	CBT-I > SH p = <.01
		b. 	CBT-I > SH p = <.01 (1st and 2nd follow-up)
McCrae, 2019	**Sleep**		
	Self-reported sleep onset latency (SOL)	a. b.	NS NS
	Wake after sleep onset (WASO)	a. 	CBT-I+ p = <.008
		a. 	CBT-I > WLC p = <.008
		a. 	CBT-P+ p = <.008
		b. 	CBT-I- p = <.008
		b. 	CBT-P+ p = <.008

	Total Sleep Time (TST)	a. NS b. NS
	Sleep efficiency (SE)	a. CBT-I+ $p = <.008$ a. CBT-P+ $p = <.008$ a. WLC+ $p = <.008$ a. CBT-I > WLC $p = <.008$* b. CBT-I+ $p = <.008$ b. CBT-P+ $p = <.008$ b. WLC+ $p = <.008$ b. CBT-I > WLC $p = <.008$
	Sleep quality rating	a. CBT-I+ $p = <.008$ a. CBT-I > WLC $p = <.008$ a. CBT-P+ $p = <.008$ a. CBT-P > WLC $p = <.008$ b. CBT-I+ $p = <.008$ b. CBT- > WLC $p = <.008$ b. CBT-P+ $p = <.008$ b. CBT-P > WLC $p = <.008$
	Dysfunctional Beliefs and Attitudes about Sleep (DBAS)	a/b. CBT-I+ $p = <.008$ a/b. CBT-I > CBT-P $p = <.008$ a/b. CBT-I > WLC $p = <.008$
	Pain	
	Morning pain intensity (Visual Analoge Scale)	a. NS b. NS
	Evening pain intensity (Visual Analoge Scale)	a. NS b. NS
	McGill Pain Questionnaire (MPQ)	a. NS b. NS
	Pain Disability Inventory (PDI)	a. NS b. NS
	Mood	
	Back Depression Inventory-Second Edition (BDI-II)	a. NS b. NS
	State-Trait Anxiety Inventory-Form Y1 (STAI-YI)	a. NS b. NS
Miro, 2011	**Sleep**	
	Pittsburgh Sleep Quality Index (PSQI)	a. CBT-I+ $p = <.000$ b. –
	Pain	
	McGill Pain Questionnaire (MPQ)	a. NS b. –
	Mood	
	Hospital Anxiety and Depression Scale (HADS-A)	a. NS b. –
	Hospital Anxiety and Depression Scale (HADS-B)	a. NS b. –
	Impaired functioning	
	Fibromyalgia Impact Questionnaire (FIQ)	a. CBT-I+ $p = .067$ b. –
	Neuropsychological	

	Alertness (Attentional Network Test-Interactions)	a.	CBT-I+ $p < .0138$
		b.	–
	Executive functioning (Attentional Network Test-Interactions)	a.	CBT-I+ $p < .0138$
		b.	–
	Orienting (Attentional Network Test-Interactions)	a.	NS
		b.	–
McCurry, 2014	**Sleep**		
	Sleep Efficiency	a.	NS
	Insomnia Severity Index (ISI)	b.	NS
	Pain		
	Graded Chronic Pain Scale (GCPS)	a.	NS
	Arthritis Impact Measurement Scales Version 2 Short Form, Revised	b.	NS
Pigeon, 2012	**Sleep**		
	Total Wake Time (TWT)	a.	NS
		b.	–
	Total Sleep Time (TST)	a.	NS
		b.	–
	Sleep Efficiency (SE)	a.	NS
		b.	–
	Insomnia Severity Index (ISI)	a.	CBT-I > C $p = <.05$ CBT-I/P > C $p = <.05$
		b.	–
	Epworth Sleepiness Scale (ESS)	a.	NS
		b.	–
	Pain		
	Multidimensional Pain Inventory (MPI)	a.	NS
		b.	–
	Pain Disability Index (PDI)	a.	NS
		b.	–
	Fatigue		
	Multidimensional Fatigue Inventory (MFI)	a.	NS
		b.	–
	Mood		
	Center for Epidemiologic Studies Depression Scale-revised (CESD-R)	a.	CBT-I > Control $p = <.05$
		a.	CBT-I/P > Control $p = < .05$
		b.	–
Sanchez, 2012	**Sleep**		
	Total Sleep Time (TST)	a.	NS
		b.	–
	Time in bed (TIB)	a.	CBT-I+ $p = < .01$
		b.	–
	Wake percentage	a.	CBT-I+ $p = < .05$
		b.	–
	% Stage 1	a.	CBT-I + $p = < .01$
		a.	CBT-I > SH $p = < .05$
		b.	–
	% Stage 2	a.	NS
		b.	–
	% Stage 3	a.	CBT-I+ $p = < .05$
		b.	–
	% Stage 4	a.	CBT-I+ $p = < .05$
		a.	CBT-I > SH $p = < .05$
		b.	–
	Light sleep	a.	CBT-I+ $p = < .05$
		b.	–
	Deep sleep	a.	CBT-I+ $p = < .01$

		a.	CBT-I > SH p = < .05
		b.	–
	Sleep Efficiency	a.	CBT-I+ p = < .05
		b.	–
	NREM sleep latency	a.	NS
		b.	–
	REM latency	a.	NS
		b.	–
	% REM density	a.	NS
		b.	–
	Number of awakenings > 3 min	a.	NS
		b.	–
	Wake after sleep onset (WASO)	a.	NS
		b.	–
	Arousals	a.	NS
		b.	–
Tang, 2012	**Sleep**		
	Time in Bed (TIB)	a.	NS
		b.	-
	Sleep onset latency (SOL)	a.	Hybrid Group > Monitoring Group p = .05
		b.	–
	Wake after sleep onset (WASO)	a.	Hybrid Group > Monitoring Group p = .05
		b.	–
	Total sleep Time (TST)	a.	Hybrid Group > Monitoring Group p = .01
		b.	–
	Sleep efficiency (SE)	a.	Hybrid Group > Monitoring Group p = .01
		b.	–
	Insomnia Severity Index (ISI)	a.	Hybrid Group > Monitoring Group p < 0.001
		b.	–
	Pain		
	Pain Interference (BPI)	a.	Hybrid Group > Monitoring Group p = <.05
		b.	–
	Pain Intensity (BPI-PPI)	a.	NS
		b.	–
	Fatigue		
	Multidimensional Fatigue Inventory (MFI)	a.	Hybrid Group > Monitoring Group p = <.05
		b.	–
	Mood		
	Hospital Anxiety and Depression Scale - Anxiety Subscale, Anxiety subscale (HADS-A)	a.	NS
		b.	–
	Hospital Anxiety and Depression Scale - Depression Subscale, Depression subscale (HADS-D)	a.	Hybrid Group > Monitoring Group p = <.01
		b.	–
	Process measures		
	Sleep-related anxiety (APSQ)	a.	Hybrid Group > Monitoring Group p = .01
		b.	–
	Sleep beliefs (DBAS-16)	a.	Hybrid Group > Monitoring Group p = .01
		b.	–
	Pain-specific sleep beliefs (DBAS-pain)	a.	Hybrid Group > Monitoring Group p = .001
		b.	–
	Pre-sleep cognitive arousal (PSAS-cognitive)	a.	Hybrid Group > Monitoring Group p = .05
		b.	–
	Pre-sleep physiological arousal (PSAS-physiol)	a.	NS
		b.	–
	Pain catastrophizing (CIPS)	a.	Hybrid Group > Monitoring Group p = .05
	Mental defeat (PSPS)	a.	NS
		b.	–

	Medication (MQS-III)	a. NS b. –
Vitiello, 2013	**Sleep**	
	Insomnia Severity Index (ISI)	a. CBT-PI > CBT-P p = <.001 a. CBT-PI > EOC p = <.001
	Sleep Efficiency (SE)	a. CBT-P > EOC p = <.02 a. CBT-P+ p = <.006
	Pain	
	Chronic Pain Scale (CPS)	a. NS b. NS
	Others	
	Arthritis Impact Measurement Scales Version 2 Short Form, Revised	a. NS b. NS
Goldway, 2019	**Sleep**	
	Pittsburgh Sleep Quality Index (PSQI)	Real-FM+ a. p = .005 b. p = .05 Sham FM a. NS b. NS
	Fatigue	
	Fibromyalgia Impact Questionnaire (fatigue subscale)	Real-FM+ a. p = .005 b. p = .05 Sham-FM a. NS b. NS
	Pain	
	Fibromyalgia Impact Questionnaire (FIQ) Pain subscale	Real-NF a. NS b. p = .005 (+) Sham-NF a. NS b. NS
	Visual Analog Scale (VAS)	Real-NF a. NS b. p = .005 (+) Sham-NF a. NS b. NS
	McGill Pain Questionnaire, general score	Real-NF a. NS b. p = .005 (+) Sham-NF a. NS b. NS
	Mood	
	Fibromyalgia Impact Questionnaire (FIQ) depression subscale	Real-NF a. p = .05 b. NS Sham-NF a. NS b. NS
	Fibromyalgia Impact Questionnaire (FIQ) anxiety subscale	Real-NF a. p = .05 b. NS Sham-NF a. NS b. NS
	STAI-T	Real-NF a. p = .05 b. NS Sham-NF a. NS b. NS
	Beck Depression Inventory (BDI)	Real-NF a. p = .05 b. NS

		Sham-NF a. NS b. NS
Wiklund, 2018	**Sleep**	
	Insomnia Severity Index (ISI)	Exercise^{+} a. p = .020 b. 1st follow-up: p = .002 2nd follow-up: p = .001
		ACT-bsm a. NS b. 1st follow-up: NS 2nd follow-up^{+} p = .009 ($^{+}$)
		Control a. NS b. NS
	Pain	
	Pain intensity recent seven days (pain-7d) according to 11-graded numeric rating scale (NRS)	Exercise^{+} a. p = .001 b. 1st follow-up: p = .015 2nd follow-up: p = .011
		ACT-bsm^{+} a. NS b. NS
		Control^{+} a. NS b. 1st follow-up: p = .010 2nd follow-up: p = .025
	Mood	
	Hospital anxiety and depression scale, anxiety subscale (HADS-A)	Exercise $^{+}$, ACT-bsm $^{+}$, Control^{+} a. NS b. NS
	Hospital anxiety and depression scale, depression subscale (HADS-D)	Exercise $^{+}$, ACT-bsm $^{+}$, Control^{+} a. NS b. NS

Note. ACT-bsm = Acceptance- and Commitment-Based Stress Management; CBT = Cognitive Behavioral Therapy; CBT-I = Cognitive Behavioral Therapy for Insomnia; CBT-P = Cognitive Behavioral Therapy for Pain; CBT-PI = Cognitive Behavioral Therapy for Pain and Insomnia; Real-NF = Real-neurofeedback; Sham-NF = Sham-neurofeedback; SH = Sleep Hygiene.

$^{+}$ indicates improvement

$^{-}$ indicates decreasement

> indicates significantly greater than

\- indicates not applicable

Table 5
Outcomes of Pharmacological Interventions

First author article, year of publication	Measures	Results Differences between mean scores before and after treatment
Ware, 2010	**Sleep**	
	Insomnia Severity Index (ISI)	Nabilone > amitriptyline
	Leeds Sleep Evaluation Questionnaire (LSEQ)	NS
	Pain	
	McGill Pain Questionnaire (MPQ)	NS
	Mood	
	Profile of Mood States, Short Form	NS
	Quality of life	
	Fibromyalgia Impact Questionnaire (FIQ)	NS
Roth, 2012	**Sleep**	
	Wake after sleep onset (WASO)	Pregabalin > Placebo *p* = <.0001
	Total Sleep Time (TST)	Pregabalin > Placebo *p* = <.0001
	Latency to Persistent Sleep (LPS)	Pregabalin > Placebo *p* = .0447
	Sleep Efficiency (ES)	Pregabalin > Placebo *p* = <.0001
	Number of awakenings after sleep onset (wake period of at least 1 epoch duration) (NAASO1)	Pregabalin > Placebo *p* = .0135
	NAASO (wake period of at least 2 epochs' duration) (NAASO2)	Pregabalin > Placebo *p* = .0008
	Slow Wave-Sleep (SWS) (Stage 3 + Stage 4)	Pregabalin > Placebo *p* = .0024
	Wake Time During Sleep (WTDS)	Pregabalin > Placebo *p* = <.0001
	Wake Time After Sleep (WTAS)	Pregabalin > Placebo NS
	Pain	
	Daily pain (part of interactive voice recognition system)	Pregabalin > Placebo *p* = .0084
Moldofsky, 2011	**Sleep**	
	Total time awake	VLD CBP+ *p* = <.05
	Total sleep time	VLD CBP+ *p* = <.05
	Stage 1	NS
	Stage 2	VLD CBP > Placebo *p* = <.05
	Stage 3	NS
	Stage 4	VLD CBP > Placebo *p* = <.05
	REM	VLD CBP > Placebo *p* = <.05
	Sleep efficiency	NS
	Pain	
	Musculoskeletal pain	VLD CBP + *p* = <.05 VLD CBP > Placebo *p* = <.05
	Fatigue	
	7-point scale (1 = "full of energy" and 2 = "totally physically exhausted")	VLD CBP+ *p* < .05
	Tenderness	
		VLD CBP+ *p* = <.05 VLD CBP > Placebo *p* = <.05
	Mood	
	HAD-score	VLD CBP+ *p* = <.05
	HAD depression	VLD CBP+ *p* = <.05 VLD CBP > Placebo *p* = <.05

Yarlas, 2016	**Sleep**	
	MOS Disturbance	
	Trial I	BTDS 10/20 > Placebo $p < 0.01$
	Trial II	BTDS 20 > BTDS 5 $p < 0.01$
	MOS Adequacy	NS
	MOS Somnolence	NS
	MOS SPI	
	Trial I	BTDS 10/20 > Placebo $p < 0.01$
	Trial II	BTDS 20 > BTDS 5 $p < 0.05$
Goforth, 2014	**Sleep**	
	Total sleep time	ESZ > Placebo $p = < .001$
	Sleep onset latency	ESZ > Placebo $p = .017$
	Wake time after sleep onset	ESZ > Placebo $p = .0024$
	Sleep efficiency	ESZ > Placebo $p = .0001$
	Number of awakenings	ESZ > Placebo $p = .0094$
	Quality ratings	ESZ > Placebo $p = .022$
	Restedness ratings	NS
	Insomnia Severity Index score	ESZ > Placebo $p = .033$
	Pain	
	Visual analog scale of pain (diaries)	ESZ > Placebo $p = .004$
	Patient Global Impression of Pain (diaries)	NS
	Clinical Global Impression of Pain	NS
	Functioning	
	Hamilton Rating Scale for Depression	ESZ > Placebo $p = .024$
	Roland Morris Low Back Pain Inventory Score	NS
Russell, 2019	**Sleep**	
	11-point Numeric Rating Scale (NRS)	
	1056 study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo $p = < .001$
	1077 study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo $p = < .001$
	MOS Sleep Disturbance	
	1056 study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo $p = < .004$
	1077 study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo $p = < .001$
	MOS Snoring	NS
	MOS Awaken Short of Breath or With Headache	
	1056 Study	Pregabalin 450 mg/day, and 600 mg/day > Placebo $p = <.026$
	1077 Study	NS
	MOS Quantity of Sleep	
	1056 Study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo $p = > .022$

	1077 Study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo *p* = > .003
	MOS Sleep Adequacy	
	1056 Study	Pregabalin 300 mg/day, 450 mg/day *p* = > .005
	1077 Study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo *p* = > .032
	MOS Daytime Somnolence	
	1056 Study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo *p* = < .04
	1077 Study	NS
	MOS Sleep Problems Index	
	1056 Study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo *p* = < .017
	1077 Study	Pregabalin 300 mg/day, 450 mg/day, and 600 mg/day > Placebo *p* = < .013
Moldofsky, 2010	**Sleep**	
	Total sleep time	NS
	Sleep onset latency	NS
	Wake after sleep onset	SXB 4.5 mg/day NS SXB 6 mg/day *p* = .032
	No. awakenings	NS
	Sleep efficiency	NS
	Rapid Eye Movement (REM)	SXB 4.5 mg.day *p* = .003 SXB 6 mg/day *p* = .027
	Non-REM	SXB 4.5 mg/day NS SXB 6 mg/day *p* = <.001
	Stage 1	NS
	Stage 2	SXB 4.5 mg/day NS SXB 6 mg/day *p* = .030
	Slow-wave sleep	SXB 4.5 mg/day NS SXB 6 mg/day *p* = .026
	Phase A1 CAP rate	NS
	Phase A2/A3 CAP rate	SXB 4.5 mg/day NS Sodium Oxybate 6 mg/day *p* = .007
	Functioning	
	Functional Outcome of Sleep Questionnaire (FOSQ)	SXB 4.5 mg/day > Placebo *p* = .027 SXB 6 mg/day > Placebo *p* = .028
	SF-36 Vitality domain	SXB 4.5 mg/day > Placebo *p* = .016 Sodium Oxybate 6 mg/day > Placebo *p* = .003
	Fibromyalgia Impact Questionnaire (FIQ)	SXB 4.5 mg.day > Placebo *p* = .009 Sodium Oxybate 6 mg/day > Placebo *p* = .001

Note. ESZ = eszoclopine; NS = not significant; SXB = Sodium Oxybate; VLD CBP = very low doses of cyclobenzaprine

> indicates significantly greater than

+ indicates improvement

Table 6
Outcomes of non-Pharmacological Treatments

Vagharseyyedin, 2019	**Sleep**	
	Pittsburg Sleep Quality Index (PSQI)	NS
	Fatigue	
	Fatigue Severity Scale (FSS)	NS

Table 7
Quality Assessment

First author, year	Selection bias *Random sequence allocation*	Selection bias *Allocation concealment*	Performance bias *Blinding of participants*	Performance bias *Blinding of personnel*	Detection bias *Blinding of outcome assessment*	Attrition bias *Incomplete outcome data*	Reporting bias *Selective reporting*	Other bias *Other sources of bias*
Goforth, 2014								
Goldway, 2019								
Jungquist, 2010								
Lami et al, 2018								
Martinez, 2013b								
McCrae, 2019								
McCurry, 2014								
Miro, 2011								
Moldofsky, 2010								
Moldofsky, 2011								
Pigeon, 2012								

Table 7
Quality Assessment Continued

First author, year	Selection bias *Random sequence allocation*	Selection bias *Allocation concealment*	Performance bias *Blinding of participants*	Performance bias *Blinding of personnel*	Detection bias *Blinding of outcome assessment*	Attrition bias *Incomplete outcome data*	Reporting bias *Selective reporting*	Other bias *Other sources of bias*
Roth, 2012								
Russell, 2009								
Sanchez, 2012								
Tang, 2012								
Vagharseyyedin, 2019								
Vitiello, 2013								
Ware, 2010								
Wiklund, 2018								
Yarlas, 2016								

Low risk of bias
Unclear risk of bias
High risk of bias

Discussion

Main Findings

The aim of the current systematic review was to provide an overview of existing interventions for sleep problems in chronic pain populations. Studies were found to examine the effectiveness of behavioral therapeutic interventions (cognitive behavioral therapy, exercise, acceptance- and commitment-based stress management, and neurofeedback), pharmacological interventions (eszopiclone, low dose cyclobenzaprine, sodium oxybate, pregabalin, naboline and amitriptyline, and buprenorphine transdermal system) and an alternative medicine intervention (acupressure).

For behavioral therapeutic interventions, it can be concluded that the majority of the interventions in the included studies were effective in improving either sleep and pain or sleep alone after treatment. However, for most studies, these results were not maintained at follow-up. Since chronic pain is a condition that persists over a longer period of time, it is important that improvements persist after treatment. In this regard, two out of 12 behavioral therapeutic interventions showed statistically significant improvements in sleep and pain outcomes after the treatment that persisted at follow-up (Martinez et al., 2013b; Wiklund et al., 2018). First, in the trial of Martinez et al. (2013b), CBT-I obtained significantly greater improvements than sleep hygiene after treatment in subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency and sleep disturbances, and these improvements were maintained at follow-up. Moreover, subjects exhibited a significant improvement after treatment in chronic pain-related self-efficacy, which persisted at two follow-ups (Martinez et al., 2013b). Self-efficacy is defined as the expected success in performing behaviors required to accomplish a desired outcome (Bandura, 1977). Social learning theories suggest that a person's self-efficacy expectations influences his or her adjustment to a major life stressor, such as chronic pain (Anderson et al., 1995). Research on self-efficacy among adults experiencing chronic pain has found that a higher level of self-efficacy is related to decreased emotional difficulties, greater pain acceptance, fewer avoidance behaviors, increased use of adequate coping mechanisms, lower physical impairment and an improvement in functioning (Logan, 2017). Lower self-efficacy among adults experiencing chronic pain, on the other hand, is related to heightened levels of pain and more frequent pain behaviors over time, resulting in a substantial burden for caregivers. Self-efficacy is thus an important attribute for the psychological and physical functioning of adults with chronic pain. Other outcome measures in the trial of Martinez et al. (2013b) support these findings, with CBT-I achieving a significant reduction after treatment and at follow-up in depression and impaired functioning. Given this finding, it is plausible that

self-efficacy not only results in an improvement of sleep but also in pain and in other domains. However, no final conclusions can be made regarding this assumption based on the trial of Martinez et al. (2013b).

In addition to CBT-I, physical exercise also had a significant positive effect on sleep and pain outcomes after treatment, and these findings persisted for up to twelve months (Wiklund et al., 2018). However, these results could not be interpreted as clinically significant. Physical exercise could be considered as a side-effect of sleep (exercise results in physiological fatigue and hence improves sleep (Wiklund et al., 2018)), but future research is required to further examine this potential.

Taking a closer look at the results, it is remarkable that Goldway et al. (2019) found delayed improvements (i.e., 16.2 ± 8.72 months after treatment) in pain in real-neurofeedback, while significant results in sleep were obtained immediately after treatment and were maintained at follow-up. Behavioral and neural learning processes can explain these latent effects. First of all, neurofeedback can be considered as a skill. By applying this skill more often in daily life, individuals continue to practice and thereby improve symptoms and neural regulation (Wiklund et al., 2018). Second, consolidation and reconsolidation processes that underlie learning processes improve over time, regardless of practice. Therefore, it is likely that synchronization or desynchronization of the targeted brain process increase over time (Wiklund et al., 2018). Furthermore, it is also remarkable that the trial of McCrae et al. (2019) found significant results after treatment and at follow-up in sleep outcomes alone (wake-after-sleep onset, sleep efficiency and sleep quality rating). In subjects receiving CBT-I, improvements in clinical pain occurred at follow-up, and no changes in clinical pain were observed in subject receiving CBT-P. These findings are not surprising given contradictions in the literature. Research has shown that both CBT-I (Martinez et al., 2019) and CBT-P (Goldenberg et al., 2004) are promising for reducing clinical pain, but findings often reveal a greater reduction in pain-related symptoms than in clinical pain itself. In addition, if pain reductions in clinical pain were found, they were often small. In light of this, one explanation for the findings of McCrae et al. (2019) is that their trial was not designed to detect small changes in pain.

In summary, for behavioral therapeutic interventions, it can be concluded that CBT-I is a more effective than real neurofeedback for improving sleep and decreasing pain in the long-term among adults in chronic pain populations. In CBT-I, improvements in sleep and pain are achieved immediately after treatment and retained up to three and six months (Martinez et al., 2013b), while improvements in real neurofeedback immediately after treatment are only

obtained in sleep and a delayed improvement in pain occurs within 16.2 ± 8.72 months after treatment (Goldway et al., 2019).

For pharmacological treatments, the findings demonstrate that pregabalin (Roth et al., 2012), eszopiclone (Goforth e al., 2014) and very low dose cyclobenzaprine (Moldofsky et al., 2011) were effective in improving sleep and pain outcomes after treatment. However, all three drugs also had adverse effects. For pregabalin, subjects reported dizziness, somnolence, headache and nausea, both in the pregabalin group and placebo group; however, the adverse effects were reported to a considerably lesser extent in the placebo group (Roth et al., 2012). For eszopiclone, adverse effects were moderate headache and noncardiac chest pain. Lastly, for subjects receiving very low dose cyclobenzaprine, adverse effects were in particular headache, dry mouth, and somnolence, but these were not reported more often than subjects in the placebo group. In light of the aforementioned drugs, a few findings emerge. First of all, pregabalin seemed to be effective on more sleep parameters (nine) than eszopiclone (seven) and very low dose cyclobenzaprine (two). However, pregabalin also had more adverse effects as compared to eszopiclone and very low dose cyclobenzaprine. Second, the trial of Roth et al. (2012) (pregabalin) did not measure the effects of the drug on mood, while the trial of Goforth et al. (2014) (eszopiclone) and of Moldofsky et al. (2011) (very low dose cyclobenzaprine) did measure such effects and found reduced depression rates. Given that research assumes depression to be a contributing mechanism in the relationship between sleep problems and chronic pain, this reduction is an important finding (Tang et al., 2017). Finally, the trial of Roth et al. (2012) had a lower risk of bias as compared to the trial of Moldosfky et al. (2011) and of Goforth et al. (2014), since the latter two studies had an unclear risk of detection bias.

Limitations and Strengths

It is important to note that this systematic review has some limitations. The first limitation is that effective interventions might not be included in the systematic review due to the databases searched and the narrowness of the inclusion criteria. It might be that the selected databases did not include all data pertaining to the topic. In addition, non-English language studies were excluded from the systematic review, but it is possible that researches may have published work in other languages. Therefore, reporting bias might have occurred because not all research findings regarding the topic were included (Higgins & Green, 2012).

The second limitation to note is that the majority of the participants in the included studies had met the diagnostic criteria for fibromyalgia and were females. These findings are not surprising, given that fibromyalgia is one of the most common chronic pain conditions and

is most prevalent in females; 75% to 90% of fibromyalgia patients are females (National Fibromyalgia Association, 2019). Although gender bias is representative of patients suffering from fibromyalgia, it remains to be determined to what extent the findings are generalizable to males with fibromyalgia and individuals of both genders suffering from other types of chronic pain.

The third limitation to note is that there was no consensus across the included studies regarding measurements and this limitation hindered adequate comparison of the effectiveness of the included studies. For example, some studies (Sanchez et al., 2012; Yarlas et al., 2016; Russell et al., 2019; Moldofsky et al., 2010; Vagharseyyedin et al., 2019) examined the effectiveness of the interventions on sleep parameters alone. While improvements in sleep parameters could have had a great impact on other chronic pain-related symptoms, this point remains unclear because pain parameters were not assessed. In order to determine if and how changes in sleep parameters are related to improvements in pain parameters, it is important that future research assesses both sleep and pain parameters. Furthermore, the included studies assessed different sleep outcomes. It is, therefore, important to develop a consensus regarding good indicators of sleep. In this regard, the National Sleep Foundation (2019) states that good sleep consists of sufficient sleep of good quality. The recommended sleep duration (total sleep time) in adults varies between seven and nine hours (Leone et al., 2018). In addition, the National Sleep Foundation (2019) defines four key determinants for sleep quality: sleeping more time while in bed (i.e., at least 85% of the total time (sleep efficiency)), falling asleep in 30 minutes or less (sleep latency), waking up no more than once per night (wake-after-sleep onset), and being awake for 20 minutes or less after falling asleep (number of awakenings >5 minutes). It is important that future studies assess all these sleep outcomes (i.e., total sleep time, sleep efficiency, sleep latency and number of awakenings). Moreover, the included studies also used different techniques to measure these sleep outcomes, such as polysomnography, actigraphy, sleep diaries, and self-report questionnaires. Of these measures, the more objective ones (PSG and actigraphy) are desirable to obtain a complete assessment of sleep. Recent research has found, however, that chronic pain symptoms are related to participants' subjective report instead of primarily being related to objective sleep (Okifunju & Hare, 2011), which indicates that self-report measures are also important in assessing sleep complaints. Therefore, a combination of objective and subjective measures is desirable. Going further, the included studies also measured different pain outcomes. The most used questionnaires were the MPQ, the NRS, the PDI, the CPSS, and the PCS. The MPQ assesses pain quality, location, exacerbating and ameliorating factors, and the NRS focuses more on pain intensity (Dansie &

Turk, 2013). The PDI is a self-report questionnaire for measuring pain disability and interference in functional, family and social domains (Dansie & Turk, 2013). The CPSS assesses a patients' self-efficacy expectations regarding pain management, their ability to cope with and their physical function (Anderson et al., 1995). The CPSS has good psychometric properties (Martinez et al., 2013b). The PCS assesses catastrophic thoughts related to pain via three subscales: rumination, magnification, and helplessness (Lami et al., 2017). The psychometric properties of the PCS are also assessed as good (Garcıa-Campayo et al., 2008). Recent research has shown that interventions for chronic pain can reduce the amount of pain with approximately 30% to 40%. However, this is achieved in less than half of treated chronic pain patients. The majority of chronic pain patients thus continue to suffer from pain that diminishes their quality of life, resulting in substantial physical impairment and emotional distress. It has to be noted, however, that there is not a one-to-one relationship between the amount and type of chronic pain; chronic pain experience is shaped by psychological factors (e.g., beliefs and expectations) and behavioral factors (e.g., context and responses) (Dansie & Turk, 2013). For this reason, it is essential to take these mechanisms into account when assessing pain outcomes. For example, by using the CPSS and the PCS.

The fifth limitation is that, for the pharmacological studies, it is not possible to draw conclusions regarding the long-term effectiveness of the drugs because follow-up data were not obtained. Since chronic pain is a persisting condition, beneficial pharmacological treatments need prolonged administration, which is not desirable given the adverse effects of drugs and the risk of habituation and dependence. In addition, none of the pharmacological studies noted placebo effects. Placebo effects refer to the beneficial or adverse effects that occur in clinical medical context, after administration of an inert treatment or as part of active treatments, due to mechanisms such as expectancies of the patients (Evers et al., 2018). Empirical evidence demonstrates that placebo effects can substantially modulate the efficacy and tolerability of pharmacological treatments (Amazio & Pollo, 2001; Aslaksen, Zwarg, Eilertsen, & Gorecka, 2015). Nonetheless, the success of a treatment is often entirely attributed to the medicine. For studies included in this systematic review, it remains unclear to what extent placebo effects were a modulating factor in the obtained results.

The final limitation of the current systematic review is related to the quality of the included studies. The lowest risk of bias ratings was found in performance bias (i.e., blinding of participants and blinding of personnel) and detection bias (blinding of outcome assessment). However, given the nature of the interventions, masking participants and personnel was not always possible.

One strength of the current systematic review is that the search for studies was conducted in more than one database, using an extensive search string (see Appendix). Furthermore, to the knowledge of the author, this will be the first systematic review to assess the effectiveness of interventions to reduce the sleep problems of people with chronic pain. The current systematic review, thus, provides information regarding the current state of field, contributes to adequate treatment of sleep problems in chronic pain conditions and gives direction for future research on this area.

Implications for Practice and Recommendations for Future Research

The current systematic review shows that cognitive behavioral therapy for insomnia is useful for treating sleep problems in chronic pain, as well as addressing cognitive aspects, such as self-efficacy and catastrophic thoughts regarding pain, daily functioning and emotional distress (symptoms of depression). Pharmacological treatments by means of pregabalin, eszopiclone and very low doses of cyclobenzaprine were also effective in reducing sleep problems, and these changes were accompanied by significant reductions in pain severity. However, research has shown that available interventions can reduce pain levels by approximately 30% to 40%, and this occurs in less than half of treated patients. Since chronic pain is a persisting condition, the main focus in treatment should not be on decreasing pain levels but more on helping patients to cope with their condition to improve their quality of life.

Because sleep problems are a major problem due to their impact on individual and socioeconomic level and are often prevalent among chronic pain populations, future research regarding effective interventions in this context is needed to offer appropriate treatments in primary healthcare. International cooperation regarding methodological design is required to examine and compare treatments more effectively. It is important that both sleep and pain outcomes are assessed after treatment and at follow-up. Regarding measurements of sleep outcomes, total sleep time, sleep efficiency, wake after sleep onset, number of awakenings and sleep latency are recommended as primary sleep outcomes, and chronic pain-related self-efficacy and pain catastrophizing are recommended as primary pain outcomes. For sleep, both objective and subjective measures are recommended to obtain a complete assessment. Future research is needed to examine possible gender differences in response to treatments for sleep problems in chronic pain conditions and to determine if results of the current systematic review are generalizable to other chronic pain conditions.

Conclusions

The present systematic review provided evidence that cognitive behavioral therapy for insomnia seems beneficial for sleep problems in chronic pain, as well as cognitive aspects such as self-efficacy and catastrophic cognitions regarding pain, daily functioning and emotional distress (symptoms of depression). It is important that treatments for sleep problems in chronic pain populations address psychological mechanisms, such as beliefs and responses, given that chronic pain levels are only reduced in exceptional cases. By addressing psychological mechanisms, the overall quality of life of patients can be improved. In light of this, pharmacological interventions included in this systematic review are not recommended given that drugs do not address underlying psychological symptoms, have serious adverse effects and are not appropriate for long-term use given the risk of habituation and tolerance. In addition, their long-term effectiveness is lacking.

International consensus regarding methodological design (e.g., measurements and follow-up durations) is required to compare interventions for sleep problems in chronic pain populations more effectively. Future research is needed to determine to what extent the results of the current systematic review can be generalized to other chronic pain conditions and males, and to examine the effectiveness of other existing treatments for sleep problems in chronic pain populations.

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Appendix

Search terms used for PubMed database

"chronic low back pain"[Title/Abstract] OR CLBP[Title/Abstract] OR "low back pain"[Title/Abstract] OR "back pain"[Title/Abstract] OR "neck pain"[Title/Abstract] OR "pelvic pain"[Title/Abstract] OR "facial pain"[Title/Abstract] OR "musculoskeletal pain"[Title/Abstract] OR ("migraine disorders"[MeSH Terms] OR ("migraine"[Title/Abstract] AND "disorders"[Title/Abstract]) OR "migraine disorders"[Title/Abstract] OR "migraine"[Title/Abstract]) OR neuropathy[Title/Abstract] OR ("neuralgia"[MeSH Terms] OR "neuralgia"[Title/Abstract]) OR ("sciatica"[MeSH Terms] OR "sciatica"[Title/Abstract]) OR ("fibromyalgia"[MeSH Terms] OR "fibromyalgia"[Title/Abstract]) OR ("Financ Manage"[Journal] OR "Field methods"[Journal] OR "fm"[Title/Abstract]) OR "whiplash associated disorder"[Title/Abstract] OR WAD[Title/Abstract] OR "repetitive strain injury"[Title/Abstract] OR RSI[Title/Abstract] OR dystrophy[Title/Abstract] OR ("headache"[MeSH Terms] OR "headache"[Title/Abstract]) OR ("Chronic Pain"[Mesh] AND ("Chronic Pain/prevention and control"[Mesh] OR "Chronic Pain/therapy"[Mesh])) AND ("Sleep Wake Disorders/prevention and control"[Mesh] OR "Sleep Wake Disorders/therapy"[Mesh]) AND (Randomized Controlled Trial[ptyp] AND "2009/06/08"[PDat] : "2019/06/05"[PDat] AND "humans"[MeSH Terms] AND ("adult"[MeSH Terms] OR "adult"[MeSH Terms:noexp] OR "aged"[MeSH Terms])

Search terms used for PsycINFO database

("chronic pain" OR "chronic low back pain" OR CLBP OR "low back pain" OR "back pain" OR "neck pain" OR "pelvic pain" OR "facial pain" OR "musculoskeletal pain" OR migraine OR neuropathy OR neuralgia OR sciatica OR fibromyalgia OR FM OR "whiplash associated disorder" OR WAD OR "repetitive strain injury" OR RSI OR dystrophy OR headache) and (Sleep OR "Sleep Disorder*" OR "Sleep Disturbance*" OR "Sleep Wake Disorder*" OR Hypersomnia OR Insomnia OR Narcolepsy OR Parasomnias OR "Sleep Apnea" OR Sleepwalking) and ("Randomized Control* Trial*" OR RCT) and (Therap* OR Intervention OR Treatment*)

Refined by language (English), publication year (2009-2019) and age (adulthood (18 years and older), young adulthood (18-29 years), thirties (30-29 years), middle age (40-64 years), aged (65 years and older), very old (85 years and older))

Search terms used for Web of Science database

(TS=(("chronic pain" OR "chronic low back pain" OR CLPB OR "low back pain" OR "back pain" OR "neck pain" OR "pelvic pain" OR "facial pain" OR "musculoskeletal pain" OR migraine OR neuropathy OR neuralgia OR sciatica OR fibromyalgia OR FM OR "whiplash associated disorder" OR wad OR "repetitive strain injury" OR RSI OR dystrophy OR headache) AND (sleep OR "Sleep Disorder*" OR "Sleep Disturbance*" OR "Sleep-Wake Disorder*" OR hypersomnia OR insomnia OR narcolepsy OR parasomnias OR "Sleep Apnea" OR sleepwalking) AND ("Randomized Controlled Trials" OR "Randomized Controlled Trial" OR "Randomized Control Trial" OR RCT) AND (therap* OR intervention OR treatment*)))

Refined by language (English) and publication year (2009-2019)