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CLINICAL REVIEW

Cognitive behavioral therapy for insomnia in patients with chronic pain – A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Several randomized controlled trials have implemented cognitive behavioral therapy for insomnia (CBT-I) for patients with comorbid insomnia and chronic pain. This systematic review and meta-analysis investigated the effectiveness of CBT-I on patient-reported sleep, pain, and other health outcomes (depressive symptoms, anxiety symptoms, and fatigue) in patients with comorbid insomnia and chronic non-cancer pain. A systematic literature search was conducted using eight electronic databases. Upon duplicate removal, 6374 records were screened against the inclusion criteria. Fourteen randomized controlled trials were selected for the review, with twelve (N = 762 participants) included in the meta-analysis. At post-treatment, significant treatment effects were found on global measures of sleep (standardized mean difference = 0.89), pain (0.20), and depressive symptoms (0.44). At follow-up (up to 12 mo), CBT-I significantly improved sleep (0.56). Using global measures of sleep, we found a probability of 81% and 71% for having better sleep after CBT-I at post-treatment and final follow-up, respectively. The probability of having less pain after CBT-I at post-treatment and final follow-up was 58% and 57%, respectively. There were no statistically significant effects on anxiety symptoms and fatigue at either assessment point. Future trials with sufficient power, longer follow-up periods, and inclusion of CBT for pain components are warranted.

Introduction

Chronic non-malignant pain is a long-term and debilitating condition that affects 50 million adults in the USA [1,2]. Types of chronic non-malignant pain include fibromyalgia, musculoskeletal pain, osteoarthritis, and complex regional pain syndrome. Insomnia, associated with disturbed sleep and problems initiating, maintaining, or returning to sleep, is frequently reported as a comorbidity in the pain population who commonly suffer from sleep disturbance and problems initiating, maintaining, or returning to sleep [3,4]. Prior research suggests that clinical insomnia is prevalent in up to 53% of patients with chronic pain, which is higher than in the general population [4,5]. Further, up to 90% of patients with chronic pain report seeking medical attention for insomnia treatment [6,7].

Several studies report a reciprocal relationship between sleep and pain, such that sleep impairments exacerbate chronic pain, and patients with greater pain levels report more sleep complaints [8–11]. Interestingly, a growing body of research suggests that sleep is a stronger predictor of subsequent pain than vice versa [9,12]. Further, experimental studies have found that sleep disturbances contribute to the development of chronic pain, and

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Glossary of Terms

CBT-I	cognitive behavioral therapy for insomnia
CBT-P	cognitive behavioral therapy for pain
CINAHL	cumulative index of nursing and allied health literature
PRISMA	preferred reporting items for systematic reviews and meta-analyses
PROSPERO	international prospective register of systematic reviews
RCT	randomized controlled trial
SD	standard deviation
SE	sleep efficiency
SMD	standardized mean difference
SOL	sleep onset latency
TST	total sleep time
WASO	wake after sleep onset

improving sleep reduces pain intensity [9,12,13]. These findings suggest that sleep could have a causal impact on chronic pain [9], and may be an important therapeutic target in treating insomnia in patients with chronic pain.

Cognitive behavioral therapy for insomnia (CBT-I) is a non-pharmacological treatment for insomnia comprising multiple components, including sleep hygiene education, stimulus control, sleep restriction, cognitive therapy, and relaxation training [14,15]. CBT-I is the recommended initial treatment for insomnia, works to strengthen the bed/bedroom environment as a cue for sleep, establish a regular sleep schedule, and minimize thoughts and behaviors that impair sleep [16]. An increasing number of studies have sought to use CBT-I to treat comorbid insomnia in patients with chronic pain, with significant improvements reported in sleep outcomes but mixed results on pain outcomes [15,17,18]. To address the inconsistency in pain outcomes, a small number of studies have developed hybrid interventions combining CBT-I and cognitive behavioral therapy for pain (CBT-P) to effectively address both pain and insomnia symptoms [19,20]. Given that insomnia is associated with an increased risk of developing other adverse outcomes including depressive and anxiety symptoms [21–23], CBT-I could potentially prevent exacerbation of these outcomes. However, studies addressing this question have reported inconsistent findings [24–26]. To date, it is uncertain whether better sleep with CBT-I also helps improve chronic pain and other health outcomes.

The role of CBT-I in patients with chronic pain has previously been examined in narrative reviews [15,17]. It was also evaluated in a meta-analysis within a group of broadly defining non-pharmacological interventions in patients with either chronic non-cancer or cancer pain [18], To date, there is no meta-analysis conducted to specifically appraise CBT-I trials for individuals with chronic non-malignant pain. The objective of the current systematic review and meta-analysis is to assess the efficacy of CBT-I in improving patient-reported sleep and other health outcomes (e.g., pain, depressive symptoms, anxiety symptoms, and fatigue) among adults with chronic pain. While we hypothesized that CBT-I will improve sleep, our analyses were exploratory in nature with regards to the other health outcomes. We also conducted a meta-regression to determine the predictors of treatment effects.

Methods

The protocol of this systematic review was registered in the international prospective register of systematic reviews (PROSPERO) (CRD42020201264). This study was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [27].

Inclusion and exclusion criteria

The inclusion criteria for the study were: 1) randomized controlled trial (RCT), testing CBT-I as a stand-alone intervention or part of a hybrid intervention with CBT-P, in adults (>18 y), with chronic non-malignant pain (e.g., arthritis, fibromyalgia, musculoskeletal pain); 2) measures patient-reported sleep as a primary or secondary objective; 3) measures patient-reported pain as a primary or secondary objective, 4) the following components must be included to classify as CBT-I: at least one behavioral technique (e.g., stimulus control, sleep restriction) and cognitive therapy, and 5) English language. Studies exclusively containing patients with pain relating to rheumatoid arthritis, headache, cancer, palliative conditions, and traumatic brain injury were excluded to focus on the broader chronic pain population.

Literature search strategy

A systematic search was conducted by an information specialist (ME) of Medline, Medine In-Process/ePubs, Embase, Cochrane Controlled Register of Trials, Cochrane Database of Systematic Reviews, APA PsycINFO, CINAHL, and ClinicalTrials.Gov. The duration of the search was set from database inception to April 2020. The search terms included “chronic pain”, “insomnia”, and cognitive behavioral therapy”. All search terms are listed in Table S1.

Study selection

Fig. 1 illustrates the PRISMA flow diagram of the search and selection process. The literature search yielded 7772 records, and an additional record was identified from independently reviewing the citations of reviews and included articles. After removing 1399 duplicate records, 6374 records were screened. Records were

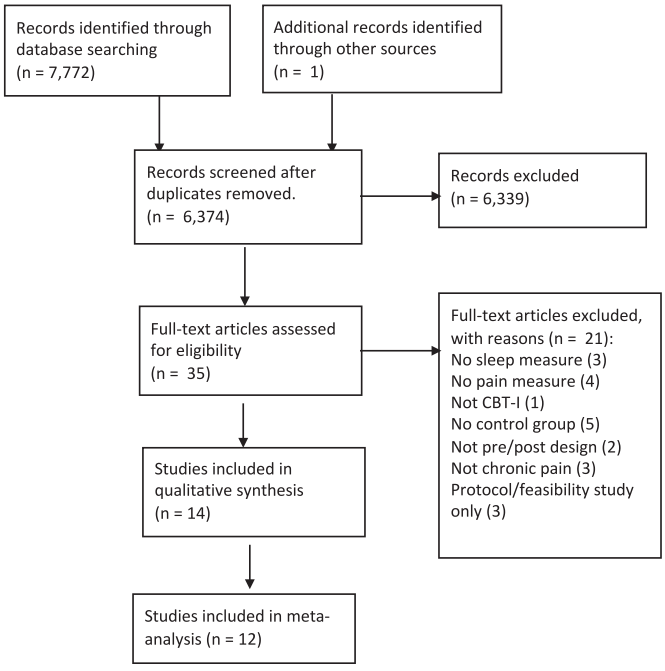


Fig. 1. PRISMA flowchart.

independently selected by two reviewers (JS, CP), who screened the titles and abstracts according to the inclusion and exclusion criteria. Thirty-five full text articles were retrieved for further examination. Disagreements between the two reviewers were resolved by consulting the senior author (FC). Upon full-text screening, 14 articles were included in the data extraction.

Data extraction and quality rating

A data extraction form was designed in Excel, and used to collect the following information: methodological (author, year of publication, country, participants, sample size, number of arms, outcome measures, quality ratings), and treatment details (components, duration and frequency, format). Data extraction was performed independently by two authors (JS, CP). Attempts were made to obtain any missing data from studies by contacting the corresponding author. Any differences in extracted data were reviewed by a third author (FC) and a consensus was reached via discussion.

For studies with multiple control arms, the least active arm was chosen. For studies with multiple active sleep intervention arms (e.g., CBT-I versus hybrid CBT-I/CBT-P), the arm comprising mostly of CBT-I components was chosen [19]. When multiple global measures (i.e., questionnaires) were used to evaluate the same outcome, data for the assessment used most commonly across the studies was extracted to reduce heterogeneity. The following outcomes were also extracted from studies using sleep diaries to measure sleep: sleep onset latency (SOL), wake after sleep onset (WASO), total sleep time (TST), and sleep efficiency (SE). Means and standard deviations (SD) of the selected outcome measures were obtained for the intervention and control groups at baseline, post-treatment, and follow-up (if applicable). For studies with multiple follow-ups, data from the final follow-up was extracted.

Quality assessments were conducted independently by two authors (JS, CP), and a third author (FC) was consulted to resolve disagreement. Additionally, both screeners (JS, CP) received training from the senior author (FC) on how to utilize these assessments. The Cochrane Risk of Bias tool [28] and Yates et al. [29] quality rating assessment were used to qualitatively and quantitatively determine study quality, respectively. For the Cochrane tool, studies received a “low”, “high”, or “unclear” rating for each risk category. The domain “blinding of participants and personnel” was removed from the quality assessment. Given that CBT-I and other nonpharmacological treatments require active involvement with the therapeutic materials, participants and therapists are never truly blinded to the group assignment [18]. The Cochrane tool has shown adequate inter-rater reliability for RCTs in patients with neck pain [30]. The Yates quality rating scale evaluates the treatment and methodological quality of RCTs for psychological treatments and has demonstrated adequate validity and inter-rater reliability [29]. The total score of the scale is 35 (nine for treatment + 26 for methodology), and two raters reported scores of 22.70, 18.71, and 12.10 as “excellent”, “average”, and “poor” psychological trials for chronic pain [29].

Data analysis

For trials with multiple publications, the article stating the main and most relevant analysis was included in the meta-analysis [26,31–33]. A random-effects model was used to calculate standardized mean differences (SMD) between scores at post-treatment (baseline - post-treatment) and final follow-up (baseline - follow-up) for each group. Then, these SMD values (SD = 1) were entered into a random-effects model to calculate SMD values between the CBT-I and control groups at post-treatment and follow-up. Confidence interval (CI) and prediction intervals (95%) were determined for SMD. We used the number of studies, SMD, upper value of the 95% CI and Tau^2 was used to calculate the predictive interval. The probability of the benefit of the treatment was calculated using the Z table statistics.

Publication bias was assessed using the Egger's test and Begg's test. The I^2 statistic was used to examine heterogeneity for each outcome (excluding sleep diary variables). Sensitivity analysis or influential analysis was performed to explore the heterogeneity, where one study was excluded each time to recalculate I^2 and end estimate. Planned subgroup analyses were conducted to compare treatment effects between group versus individually delivered CBT-I for each outcome (excluding sleep diary variables) and assessment point. Meta-regression analyses were performed *a priori* to determine whether the following dichotomous factors predicted treatment effects on global measures of sleep: study quality by Cochrane risk assessment (some concerns vs. low concerns), Yates quality rating scale ≥25 (yes vs. no), loss of patients at post-treatment (yes vs. no), CBT-I format (group vs. individual), and sample size >50 (yes vs. no). Meta-analyses were conducted using RevMan 5.4 and the meta-regression was performed with Comprehensive Meta-Analysis Software.

Results

Study characteristics

Table 1 presents the study characteristics of the 14 RCTs included in the systematic review. Studies were conducted in Canada (n = 1), Spain (n = 3), UK (n = 1), and the USA (n = 9). Twelve of these studies were included in the meta-analysis, comprising 762 participants (range of 20–367 participants, mean age: 45–73.1 y, female: 55%–100%) [19,20,24–26,33–39].

Four studies involved participants with different types of chronic non-malignant pain, with three utilizing a physician or physical examination to confirm chronic pain diagnosis [19,20,24,25]. Another five studies comprised of individuals with fibromyalgia who met the American College of Rheumatology criteria for fibromyalgia [26,32,33,36,37,40]. The remaining five studies were conducted in persons with osteoarthritis [31,33,35,38,39], and the diagnosis confirmed by radiographic or physician examination in three of these studies [35,38,39].

The diagnostic criteria for insomnia was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R, DSM-IV and DSM-IV-TR) manual [41–43] in five studies [24,26,32,34,36], and the Research Diagnostic Criteria for Insomnia in four studies [31,33,35,38,44]. The remaining five RCTs utilized a combination of self-reported criteria that varied in duration, frequency, and included outcomes (e.g., sleep onset latency, wake after sleep onset, total sleep time) [19,20,25,37,39]. Two studies also included the Insomnia Severity Index in their insomnia diagnostic criteria (≥10 [35] and ≥15 [19]). Five studies utilized polysomnography to rule out for other sleep disorders (e.g., sleep apnea) [19,25,32,34,39].

All RCTs involved multimodal CBT-I, although our inclusion criteria only required at least one behavioral and one cognitive technique (Table 2). The common components include: sleep education, sleep hygiene, sleep restriction, stimulus control, cognitive therapy, and relaxation training. Four RCTs utilized a combined CBT-I and CBT-P (e.g., cognitive therapy for pain, pain education, reducing pain catastrophizing and safety seeking behavior, and relaxation) [20,31,33,36]. The frequency and duration of CBT-I ranged from 4 to 10 wk and 15–120 min per week, respectively. All CBT-I interventions were conducted in a face-to-face medium, with seven trials performed in a group (4–12 participants per group) [24,26,31–33,36,39] and seven trials used an individual format [19,20,25,34,35,37,38]. The control arms were comprised of

Table 1
Study characteristics.

Author Year (Country)	Pain Condition and Diagnosis	Insomnia Diagnosis	N	Age, mean (years)	Female (%)	Assessment points	Global Measures	Yates Quality Rating
Currie et al. (2000) [24] (Canada)	Chronic pain: back (72%), neck (20%), lower limbs (5%), pelvic (3%) Dx: specialist in physical medicine	DSM-IV	60	45	55	Baseline, post-Rx, 3-mo follow-up	Sleep: PSQI Pain: MPI-PS Depressive symptoms: BDI Anxiety symptoms: None Fatigue: None	Rx: 9 Methodology: 16.5 Overall: 25.5
Edinger et al. (2005) [34] (USA)	FM (100%) Meet the American College of Rheumatology criteria for FM. Dx: rheumatologist	DSM-III-R; sleep diary; and PSG	47	48.6	95.7	Baseline, post-Rx, 6-mo follow-up	Sleep: ISQ Pain: MPQ Depressive symptoms: None Anxiety symptoms: None Fatigue: None	Rx: 8 Methodology: 17.5 Overall: 25.5
Heffner et al. (2018) [35] (USA)	Knee OA (100%) Dx: radiographic evidence or physician confirmation	Research diagnostic criteria for insomnia; ISI	30	61	60	Baseline, post-Rx	Sleep: ISI Pain: WOMAC Index Depressive symptoms: None Anxiety symptoms: None Fatigue: None	Rx: 2.5 Methodology: 9.5 Overall: 12
Jungquist et al. (2010) [25] (USA)	Chronic pain: lower back (64%), neck (32%), and thoracic spinal level (4%) Dx: physical examination, urinalysis, and bloodwork	SOL > 30 min and/or WASO > 30 min for > 3 d/wk for > 6 mo; PSG	28	48.7	78	Baseline, post-Rx	Sleep: ISI Pain: MPI-PS Depressive symptoms: BDI Anxiety symptoms: None Fatigue: None	Rx: 9 Methodology: 16.5 Overall: 25.5
Lami et al. (2018) [36] (Spain)	FM (100%) Meet the American College of Rheumatology criteria for FM for > 6 mo	DSM-IV-TR	113	50.2	100	Baseline, post-Rx, 3-mo follow-up	Sleep: PSQI Pain: MPQ-SF-VAS Depressive symptoms: SCL-90-R-D Anxiety symptoms: SCL-90-R-A Fatigue: MFI	Rx: 7 Methodology: 19.5 Overall: 26.5
Martinez et al. (2013) [26] (Spain)	FM (100%) Had to meet the American College of Rheumatology criteria for FM for > 6 mo	DSM-IV-TR	59	47.6	100	Baseline, post-Rx, 3- and 6-mo follow-up	Sleep: PSQI Pain: MPQ-SF-VAS Depressive symptoms: SCL-90-R-D Anxiety symptoms: SCL-90-R-A Fatigue: MFI	Rx: 7.5 Methodology: 19 Overall: 26.5
McCrae et al. (2019) [37] (USA)	FM (100%) Diagnosis: tender point testing; Meet the American College of Rheumatology criteria for FM for > 6 mo	SOL > 30 min or WASO > 30 min for at least 3 d per wk for > 6 mo; Sleep diary	113	53	97.3	Baseline, post-Rx, 6-mo follow-up	Sleep: Not applicable Pain: MPQ Depressive symptoms: BDI Anxiety symptoms: STAI-Y1 Fatigue: None	Rx: 8.5 Methodology: 21.5 Overall: 30
McCurry et al. (2014) [31] (USA)*	OA (100%) Medical care for OA in the prior 3 y; Significant arthritis pain as defined by Grade II, III, or IV pain on the Graded Chronic Pain Scale	Self-reported sleep difficulties for 3 or more nights per wk during the past month with at least one daytime sleep-related problem; Research diagnostic criteria for insomnia	367	73.1	78.2	Baseline, 18-mo follow-up	Sleep: ISI Pain: GCPS Depressive symptoms: GDS Anxiety symptoms: None Fatigue: None	Rx: 8 Methodology: 20 Overall: 28
Miro et al. (2011) [32] (Spain)*	FM (100%) Meet the American College of Rheumatology criteria for FM; FM Dx by medical exam.	DSM-IV; Interview; Questionnaires; Neuropsychological test; PSG	31	46.5	100	Baseline, post-Rx	Sleep: PSQI Pain: MPQ-SF-VAS Depressive symptoms: HADS-D Anxiety symptoms: HADS-D Fatigue: None	Rx: 7 Methodology: 16 Overall: 23**
Pigeon et al. (2012) [19] (USA)	Chronic pain: spine, shoulders, hips, or limbs Pain for > 6 mo; patients had a physical examination with ECG, clinical chemistries and toxicology screens	SOL and/or WASO 30 min or longer for > 3 d per wk for 6 mo or longer; PSG	21	50.7	66.7	Baseline, post-Rx	Sleep: ISI Pain: MPI Depressive symptoms: CEDS-Revised Anxiety symptoms: None Fatigue: MFI	Rx: 4.5 Methodology: 11.5 Overall: 16**
Smith et al. (2015) [38] (USA)	Knee OA (100%) Meet the American College of Rheumatology criteria for knee OA; Dx: rheumatologist plus	Research diagnostic criteria for insomnia; Symptoms lasting >1 mo, > 2 nocturnal awakenings lasting	100	59.4	79	Baseline, post-Rx, 3- and 6-mo follow-up	Sleep: ISI Pain: WOMAC Index Depressive symptoms: None	Rx: 5.5 Methodology: 19.5 Overall: 25

	radiographic evidence of knee OA, knee pain ratings, and stable dose of NSAIDs.	>15 min, or WASO and/or SOL >30 min					Anxiety symptoms: None Fatigue: None	
Tang et al. (2012) [20] (UK)	Chronic pain: MSK pain (85%), OA (35%), RA (10%), complex regional pain syndrome (10%), headache (10%), and FM (5%) Pain for > 6 mo; moderate severity based on BPI	ISI; SOL or WASO 30 min or longer for 3 or more nights per wk for one mon or longer	20	48.5	90	Baseline, post-Rx, 1-mo, 6-mo follow-up	Sleep: ISI Pain: BPI-PI Depressive symptoms: HADS-D Anxiety symptoms: HADS-A Fatigue: MFI	Rx: 6.5 Methodology: 17.5 Overall: 24**
Vitiello et al. (2009) [39] (USA)	OA (100%) Dx: radiograph or MRI; Receiving physician Rx; Moderate pain rating on SF-36 pain item, or pain item from the Arthritis Impact Measurement Scales 2	At least 3 episodes of insomnia per wk for at least 6 mo (defined as SOL 30 min or longer, WASO 60 min or longer, total sleep time < 6.5h per night); PSG	51	67.7	88.2	Baseline, post-Rx, 12-mo follow-up	Sleep: Not applicable Pain: MPQ-SF Depressive symptoms: GDS Anxiety symptoms: None Fatigue: None	Rx: 5 Methodology: 14.5 Overall: 19.5
Vitiello et al. (2013) [33] (USA)	OA (100%) Medical care for OA in the prior 3 y: Significant OA pain as defined by Grade II, III, or IV pain on the Graded Chronic Pain Scale	Self-reported sleep difficulties for 3 or more nights per wk during the past mon with at least one daytime sleep-related problem; research diagnostic criteria for insomnia	367	73.1	78.5	Baseline, post-Rx, 9-mo follow-up	Sleep: ISI Pain: GCPS Depressive symptoms: GDS Anxiety symptoms: None Fatigue: None	Rx: 8 Methodology: 18 Overall: 26

Abbreviations: BDI, Beck Depression Inventory; BPI-PI, Brief Pain Inventory Pain Interference subscale; CEDS-Revised, Center for Epidemiologic Studies Depression Scale Revised; DBAS, Dysfunctional Beliefs and Attitudes about Sleep; DSM-III-R, American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders Third Edition, revised; DSM-IV, American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorder Fourth Edition; DSM-IV-TR, American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorder Fourth Edition, Text Revision; FM, fibromyalgia; GCPS, Graded Chronic Pain Scale; GDS, Geriatric Depression Scale; HADS-A, Hospital Anxiety and Depression Scale Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale Depression subscale; ISI, Insomnia Severity Index; ISQ, Insomnia Symptom Questionnaire; MFI, Multidimensional Fatigue Inventory; MPI, Multidimensional Pain Inventory; MPI-PS, Multidimensional Pain Inventory Pain Severity subscale; MPQ, McGill Pain Questionnaire; MPQ-SF-VAS; McGill Pain Questionnaire Short Form Visual Analogue Scale; MPQ-SF; McGill Pain Questionnaire Short Form; OA, osteoarthritis; PSG; polysomnography; PSQI; Pittsburgh Sleep Quality Index; SCL-90-R-A, Symptom Checklist-90-Revised Anxiety subscale; SCL-90-R-D, Symptom Checklist-90-Revised Depression subscale; SE, sleep efficiency; SOL, sleep onset latency; STAI-Y1, State-Trait Anxiety Inventory-Form Y1; WASO, wake after sleep onset; VAS, visual analogue scale; WOMAC Index; Western Ontario and McMaster Universities Osteoarthritis Index. *Study was not included in the meta-analysis, results from main trial article was included in analyses. **Pilot trial did not calculate power and sample size.

passive (e.g., waitlist control, usual medical care, contact control) [19,24,33,35–37], and active interventions (e.g., sleep hygiene, education, contact control, behavioral desensitization, symptom monitoring, attention control) [20,25,26,31–33,38,39].

All but three studies reported sleep, pain, and at least one other health outcome at baseline and post-treatment [34,35,38]. The follow-up period ranged from 3 to 18 mo.

Quality assessment

The quantitative assessments using the Yates quality rating scale demonstrated a mean treatment score of 6.8 (SD: 1.83, range: 2.5 to 9), mean methodology score of 16.7 (SD: 3.23, range: 9.5 to 21.5), and mean overall score of 23.5 (SD: 4.77, range: 12 to 30) (Table 1).

Using the Cochrane tool, all studies had a low or unclear bias on all domains (Fig. S1). Random sequence generation was the most sufficiently addressed, with all but three studies reporting low bias in this domain [34,35,38]. Allocation concealment was the least sufficiently addressed, with only five studies reporting low bias in this domain [20,26,32,36,37].

Meta-analysis

Sleep

Ten studies contributed 644 participants to analyses on global measures of sleep [19,20,24–26,33–36,38]. The Insomnia Severity Index was the most commonly used measure of sleep [45]. Other global measures of sleep included the Pittsburgh Sleep Quality Index [46], and Insomnia Symptom Questionnaire [47]. Across all outcome measures of sleep, CBT-I caused significant large effects at post-treatment (SMD = 0.89, [95% Confidence Interval: 0.53, 1.25], $p < 0.00001$) (Fig. 2a). The 95% prediction interval was −0.24 to 2.02. Both Egger's Test and Begg's test showed evidence of publication bias on post-treatment effects of sleep ($p < 0.005$), but no publication bias was apparent at follow-up. Given that significant heterogeneity was found between studies at post-treatment, a sensitivity analysis detected Jungquist et al. [25] and Vitiello et al. [33] as potential sources of heterogeneity. Excluding studies decreased the I^2 statistic from 73% to 37% and the overall treatment effect on sleep remained significant (0.86 [0.57, 1.15], $p < 0.00001$) (Table 3). Subgroup analyses demonstrated that the efficacy of CBT-I remained largely significantly for both group-based [24,26,33,36] and individual-based [19,20,25,34,35,38] interventions at post-treatment (Table 3).

Six studies contributed data from 567 participants on sleep at follow-up (range: three to nine months) [24,26,33,34,36,38]. There was a large significant treatment effect of CBT-I at final follow-up (0.56 [0.25, 0.87], $p = 0.0004$) (Fig. 2b). The 95% prediction interval was −0.38 to 1.50. Significant heterogeneity was found with an I^2 statistic of 64%. Removing Currie et al. [24] decreased the heterogeneity to a nonsignificant I^2 statistic of 18%, and the overall treatment effect remained largely significant (0.40 [0.19, 0.61], $p = 0.0001$) (Table 3). Subgroup analyses showed that group-[24,26,33,36] and individual-based [34,38] CBT-I demonstrated significant effects at follow-up (Table 3). In comparison to controls, the probability of having better sleep after CBT-I was 81% and 71% at post-treatment and final follow-up, respectively.

Seven studies contributed to pooled analyses assessing the effects of CBT-I on SOL and WASO at post-treatment (n = 358) [20,24,25,34,37–39], and four studies involving 259 participants contributed to analyses at follow-up (range: three to six months) [24,34,37,38]. In comparison to controls, CBT-I elicited significant effects on SOL at post-treatment (1.06 [0.48, 1.64], $p = 0.0003$) and follow-up (1.08 [0.13, 2.04], $p = 0.03$) (Figs. S2a and b). The prediction intervals for SOL at post-treatment and follow-up

Table 2
CBT-I and control arm components.

Author, Year	Number of Arms: Description of Arms	Frequency (Duration)	Medium	Format
Currie et al. (2000) [24]	Two arms: CBT-I vs. wait-list control	7 weekly sessions (120 min)	Face-to-face	Group (5–7 individuals)
Edinger et al. (2005) [34]	Three arms: CBT-I vs. sleep hygiene vs. usual Care	6 weekly sessions (1st lasted 45–50 min and subsequent ones 15–30 min)	Face-to-face	Individual
Heffner et al. (2018) [33]	Two arms: CBT-I vs. control	6 weekly sessions (1st lasted 90 min and subsequent ones 60 min)	Face-to-face	Individual
Jungquist et al. (2010) [25]	Two arms: CBT-I vs. contact control	8 weekly sessions (30–90 min)	Face-to-face	Individual
Lami et al. (2018) [36]	Three arms: CBT-P vs. CTP-IP vs. usual medical care	9 weekly sessions (90 min)	Face-to-face	Group (5–7 individuals)
Martinez et al. (2013) [26]	Two arms: CBT-I vs. sleep hygiene	6 weekly sessions (90 min)	Face-to-face	Group (5–6 individuals)
McCrae et al. (2019) [37]	Three arms: CBT-I vs. CTP-P vs. wait-list control	8 weekly sessions (50 min)	Face-to-face	Individual
McCurry et al. (2014) [31]	Three arms: CBT-P vs. CTP-IP vs. education-only Control	6 weekly sessions (90 min)	Face-to-face	Group (5–12 individuals)
Miro et al. (2011) [32]	Two arms: CBT-I vs. sleep hygiene	6 weekly sessions (90 min)	Face-to-face	Group (5–6 individuals)
Pigeon et al. (2012) [19]	Four arms: CBT-P vs. CBT-I vs. CBT-IP vs. wait-list control	10 weekly sessions (50–60 min)	Face-to-face	Individual
Smith et al. (2015) [38]	Two arms: CBT-I vs. behavioral desensitization	8 weekly sessions (45 min)	Face-to-face	Individual
Tang et al. (2012) [20]	Two arms: CBT-IP vs. symptom monitoring	4 weekly sessions (120 min)	Face-to-face	Individual
Vitiello et al. (2009) [39]	Two arms: CBT-I vs. attention control	8 weekly sessions (120 min)	Face-to-face	Group (4–8 individuals)
Vitiello et al. (2013) [33]	Three arms: CBT-P vs. CTP-IP vs. education-only control	6 weekly sessions (90 min)	Face-to-face	Group (5–12 individuals)

Abbreviations: CBT, cognitive behavioral therapy; CBT-I, cognitive behavioral therapy for insomnia; CBT-IP, cognitive behavioral therapy for insomnia and pain; CBT-P, cognitive behavioral therapy for pain.

were −0.85 to 2.97 and −3.28 to 5.44 respectively. Additionally, significant treatment effects on WASO were observed at post-treatment (1.00 [0.53, 1.47], $p < 0.0001$) and follow-up (0.87 [0.13, 1.60], $p = 0.02$) (Figs. S2c and d). The prediction intervals for WASO at post-treatment and follow-up were −0.47 to 2.47 and −2.43 to 4.17 respectively. Eight studies contributed to pooled analyses assessing the effects of CBT-I on TST and SE at post-treatment ($n = 368$) [19,20,24,25,34,37–39], and four studies involving 259 participants contributed to analyses at follow-up (range: three to six months) [24,34,37,38]. No significant treatment effects were found on TST at post-treatment (−0.11 [−0.39, 0.16], $p = 0.41$) or follow-up (−0.43 [−0.88, 0.02], $p = 0.06$) (Figs. S2e and f). The prediction intervals for TST at post-treatment and follow-up were −0.75 to 0.53 and −0.43 to −2.26 respectively. Compared with controls, CBT-I resulted in significant improvements on SE at post-treatment (−1.25 [−1.76, −0.74], $p < 0.00001$) and follow-up (−1.10 [−1.90, −0.31], $p = 0.006$) (Figs. S2g and h). The prediction intervals for SE at post-treatment and follow-up were −2.85 to 0.35 and −4.65 to 2.45 respectively.

Pain

All studies contributed to pooled analyses assessing the effects of CBT-I on pain at post-treatment ($n = 783$). The McGill Pain Questionnaire (full and short form) was the most commonly used measure [48,49]. There were large significant treatment effects on pain at post-treatment (0.20 [0.06, 0.34], $p = 0.006$) (Fig. 2c). The 95% prediction interval was 0.04–0.35. There was no significant heterogeneity between studies. Subgroup analyses demonstrated a significant treatment effect for group-based [24,26,33,36,39] CBT-I ($p = 0.01$), but not individual-based [19,20,25,34,35,37,38] CBT-I (Table 3). Post-hoc analyses revealed significant post-treatment effects in studies assessing pain intensity/severity alone (0.19 [0.04, 0.34], $p = 0.01$) [24,25,33–39], and pain interference alone (0.75 [0.14, 0.37], $p = 0.02$) [20,25]. A post-hoc analysis comprising only of hybrid CBT-I/CBT-P studies also revealed a significant treatment effect at post-treatment (0.26 [0.05, 0.47], $p = 0.02$) [20,33,36].

Six RCTs contributed 583 participants to pooled analyses assessing the effectiveness of CBT-I on pain at follow-up (range: three to nine months) (Fig. 2d) [24,33,34,36–38]. There was no significant overall treatment effect (0.17 [−0.11, 0.45], $p = 0.24$). The 95% prediction interval was −0.50 to 0.84. Significant heterogeneity was found between studies, and a sensitivity analysis identified Smith et al. [38] as a potential source of heterogeneity. Excluding this study reduced the I^2 statistic from 60% to 44%, and the overall treatment effect remained non-significant (0.26 [−0.01, 0.53], $p = 0.06$) (Table 3). Similar to post-treatment, subgroup analyses on follow-up revealed a significant improvement for group-based [24,33,36] CBT-I ($p = 0.005$), but not individual-based [34,37,38] CBT-I (Table 3). Further, a post-hoc analysis comprising only of hybrid CBT-I/CBT-P studies did not find a treatment effect at follow-up [33,36]. In comparison to controls, the probability of having better pain after CBT-I was 58% and 57% at post-treatment and final follow-up, respectively.

Depressive symptoms, anxiety symptoms, and fatigue

The Beck Depression Inventory and Geriatric Depression Scale were the most commonly used measures of depressive symptoms [50,51]. Eight RCTs contributed the data of 383 participants to examine the effects of CBT-I on depressive symptoms at post-treatment [19,20,24–26,36,37,39]. There was a significant improvement on depressive symptoms at post-treatment (0.44 [0.09, 0.79], $p = 0.01$) (Fig. S3a). Excluding Jungquist et al. [25] led to a nonsignificant I^2 statistic of 44%, and the overall treatment effect was borderline significant at post-treatment (0.30 [−0.00, 0.60], $p = 0.05$) (Table 3). Subgroup analyses indicated a significant improvement on depressive symptoms from individual-based [19,20,25,37] CBT-I ($p = 0.01$), but not group-based [24,26,36,39] CBT-I (Table 3). Five RCTs contributed 325 participants to the pooled analysis on the effects of CBT-I at follow-up [24,26,36,37,39]. There was no significant overall treatment effect on depressive symptoms (Fig. S3b). No significant heterogeneity was found between studies. A subgroup analysis on group-based CBT-I did not reveal a significant treatment effect (Table 3) [24,26,36,39].

Four RCTs assessed anxiety symptoms at post-treatment ($n = 234$) [20,26,36,37], three of which ($n = 214$) contributed to the pooled analysis at follow-up [26,36,37]. There was no

significant overall effect of CBT-I on anxiety symptoms at post-treatment or follow-up (Figs. S3c and d). Subgroup analyses did not reveal significant treatment effects of group-based [26,36] or individual-based [20,37] CBT-I (Table 3). A subgroup analysis did not reveal a significant treatment effect of group-based CBT-I (Table 3) [26,36]. No significant heterogeneity was found between studies at either assessment point. Four RCTs contributed 168 participants to the pooled analysis assessing fatigue at post-treatment [19,20,26,36]. There was no significant improvement on fatigue at post-treatment (Fig. S3e). After removing Martinez et al. [26] and Lami et al. [36], the I^2 statistic decreased from 88% to 0%, and the overall treatment effect became significant (1.49 [0.65, 2.33], $p = 0.0005$) (Table 3). Subgroup analyses indicated a significant improvement on fatigue from individual-based [19,20] CBT-I ($p = 0.0005$), but not group-based [26,36] CBT-I (Table 3). Two RCTs evaluated fatigue at follow-up and contributed 128 participants to the pooled analysis [26,36]. There was no significant overall effect of CBT-I on fatigue at follow-up (Fig. S3f). No significant heterogeneity was found between studies.

Meta-regression

Meta-regression analyses are presented in Table S2. The Yates quality rating scale ≥25 significantly predicted the effectiveness of CBT-I at post-treatment, such that higher scores were associated with greater post-treatment effects on global measures of sleep. Fewer lost to follow-up significantly predicted better treatment effects at post-treatment and follow-up. Individual CBT-I predicted greater CBT-I effects at post-treatment (probability: 89% vs. 75%) and at follow-up (probability: 75% vs. 70%). The Cochrane risk assessment and a sample size >50 did not significantly predict treatment effects at either assessment points.

Discussion

Patient-reported health outcomes such as pain, depressive symptoms, anxiety symptoms, and fatigue may contribute to sleep impairment in patients with chronic pain [9,52–55]. The current study involves a focused meta-analysis on the effectiveness of CBT-I interventions on these multiple patient-reported health outcomes in adults with chronic non-malignant pain. Across 10 RCTs [19,20,24–26,33–36,38], we found that CBT-I largely improved global measures of sleep at post-treatment and follow-up, with a probability of 81% and 71% of having better sleep after CBT-I at post-treatment and final follow-up, respectively. Diary-derived SOL, WASO, and SE also improved at post-treatment and follow-up. We observed significant treatment effects on pain at post-treatment, with a probability of 58% and 57% of having less pain after CBT-I at post-treatment and final follow-up, respectively. While depressive symptoms significantly decreased at post-treatment, no significant effects were found on anxiety symptoms and fatigue.

In comparison to controls, CBT-I caused substantial improvements in global measures of sleep at post-treatment (SMD = 0.89) and follow-up (SMD = 0.56), which were maintained when studies were removed to eliminate heterogeneity [24,25,33]. This finding is consistent with Tang et al.'s [18] subgroup analysis demonstrating significant post-treatment and follow-up effects on sleep by non-pharmacological interventions (including behavioral therapy and psychoeducation) in patients with chronic non-malignant pain. Additionally, both group-based [24,26,33,36] and individual-based [19,20,25,34,35,38] CBT-I led to meaningful improvements ($p < 0.001$) in sleep at both assessment points.

Although it is well established that individual CBT-I is highly effective for improving sleep [56], our finding in chronic pain patients with comorbid insomnia is consistent with a prior meta-analysis that demonstrated medium to large effects of group CBT-I on sleep outcomes in adults with primary or comorbid insomnia [57]. Interestingly, a prior meta-analysis comprising adults with comorbid insomnia found that individual CBT-I produced stronger treatment effects [58], and aligns with our meta-regression results that individual CBT-I significantly predicted better sleep at post-treatment and follow-up. Future trials should evaluate the comparative effectiveness of individual-versus group-based CBT-I in patients with chronic pain.

Given the significant prevalence of comorbid insomnia in the chronic non-cancer population, healthcare providers should assess for insomnia symptoms in pain clinics. Due to the high prevalence of comorbid insomnia in the chronic pain population and shortage of qualified CBT-I therapists, a stepped care approach could effectively distribute resources to individuals based on the severity and prognosis of their insomnia [56]. The effectiveness of CBT-I in self-help (e.g., digital, books/manuals, audiovisual) and remote (e.g., telephone, telemedicine) are emerging in the literature, and meta-analyses have reported their efficacy on several patient-reported sleep outcomes, including the Insomnia Severity Index and sleep diary variables (e.g., SOL, WASO, and SE) [59–62]. To our knowledge, no such interventions have been tested for efficacy in the chronic non-cancer pain population, although we are aware of the ongoing OsteoArthritis and Therapy for Sleep trial (Washington, USA) that will be examining the effectiveness of a telephone CBT-I intervention for co-morbid insomnia in patients with osteoarthritis [63].

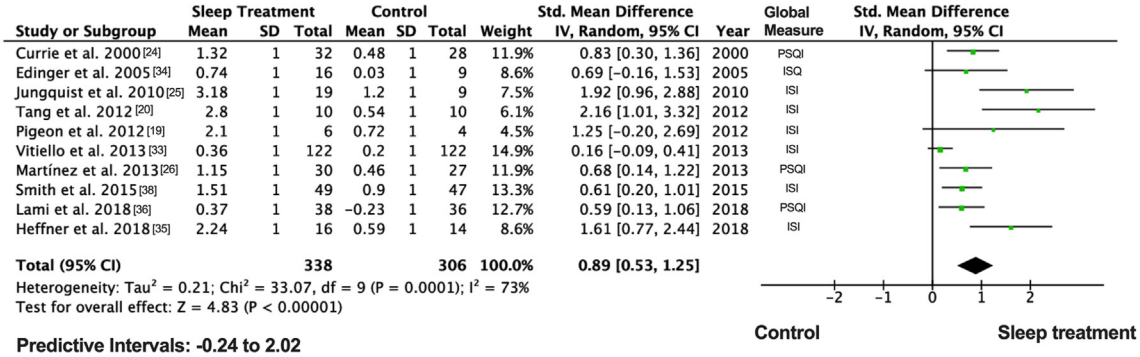
We also found a significant treatment effect on pain at post-treatment (SMD = 0.20), but not at follow-up. Individual studies reported mixed findings on changes in pain outcomes [19,20,24–26,31–39], although a recent meta-analysis found that nonpharmacological treatments caused near significant effects at post-treatment in adults with chronic non-malignant pain ($p = 0.07$) [18]. Our results are consistent with the speculation that sleep is a strong predictor of pain [9]. It is also well established that sleep deprivation can impact pain processing and experimentally inducing prolonged sleep restriction can affect pain habituation and sensitization, thereby increasing the susceptibility to chronic pain in otherwise healthy participants [8–13,64]. Further, sleep disturbances may worsen existing chronic pain conditions, while good sleep may predict pain resolution [9]. Given the mixed findings reported among individual trials, it is possible they were not adequately powered to detect a long-term effect on pain. Further, using a treatment protocol to address only insomnia and sleep habits may not be sufficient for targeting chronic pain [15].

It was suggested that the addition of CBT-P to a CBT-I protocol may effectively lead to improvement in pain [65]. As noted earlier, there is a reciprocal relationship between chronic pain and insomnia [8–11]. Longitudinal research has also shown that sleep disruption may be associated with development of a pain condition, lower physical functioning, and greater levels of inflammatory markers [66]. Many patients report pain as a primary reason for the onset of their insomnia [67–69]. Hence, hybrid treatments that combine CBT-I and CBT-P components may cause greater and more durable effects on both sleep and pain. Hybrid treatments may also allow clinicians with more flexibility and opportunities to personalize treatments to individual needs, and addressing multiple health concerns through one program can improve accessibility to services, target behavioral and cognitive processes that influence both insomnia and pain (e.g., catastrophizing or avoidant behaviors [70], and allows patients to manage comorbidities that contribute to their pain and disability [71].

Interestingly, our post-hoc analysis comprising only of hybrid CBT-I and CBT-P trials showed similar effects on pain to traditional CBT-I at post-treatment only (SMD = 0.26) [20,33,36]. However, a secondary analysis of Vitiello et al.'s [33] trial found that

Sleep

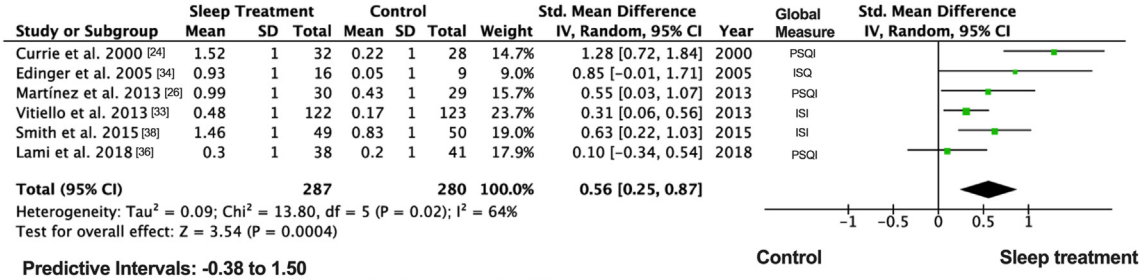
a. Baseline vs. Post-treatment between sleep treatment and control group



Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 33.07$, df = 9 (P = 0.0001); $I^2 = 73\%$
Test for overall effect: Z = 4.83 (P < 0.00001)

Predictive Intervals: -0.24 to 2.02
Probability of having a better sleep quality than control: 81%

b. Baseline vs. Follow-up between sleep treatment and control group

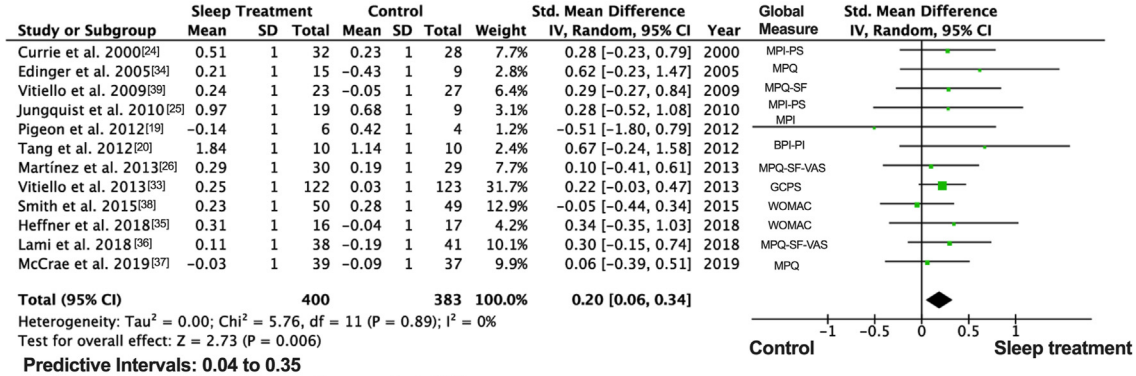


Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 13.80$, df = 5 (P = 0.02); $I^2 = 64\%$
Test for overall effect: Z = 3.54 (P = 0.0004)

Predictive Intervals: -0.38 to 1.50
Probability of having a better sleep quality than control: 71%

Pain

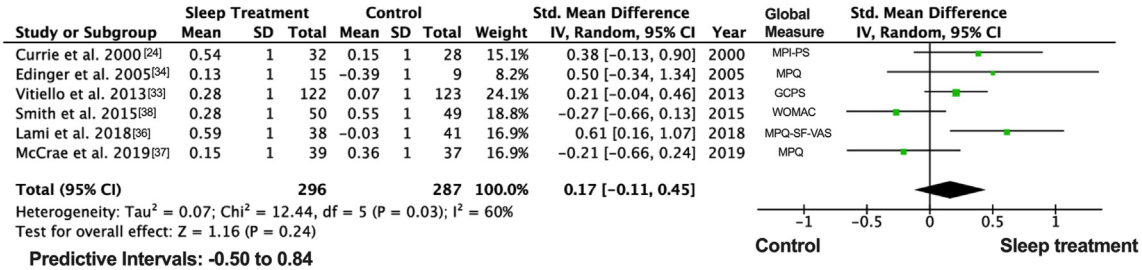
c. Baseline vs. Post-treatment between sleep treatment and control group



Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.76$, df = 11 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 2.73 (P = 0.006)

Predictive Intervals: 0.04 to 0.35
Probability of reporting less pain than control: 58%

d. Baseline vs. Follow-up between sleep treatment and control group



Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 12.44$, df = 5 (P = 0.03); $I^2 = 60\%$
Test for overall effect: Z = 1.16 (P = 0.24)

Predictive Intervals: -0.50 to 0.84
Probability of reporting less pain than control: 57%

Fig. 2. Forest plots of treatment effects on global measures of a) sleep at post-treatment, b) sleep at follow-up, c) pain at post-treatment, and d) pain at follow-up. Abbreviations: BPI-PI, Brief Pain Inventory Pain Interference subscale; GCPS, Graded Chronic Pain Scale; ISI, Insomnia Severity Index; ISQ, Insomnia Symptom Questionnaire; MPI,

Table 3
Sensitivity and subgroup analyses.

Outcome		Sensitivity Analysis			Subgroup Analysis	
		Excluded Study	Modified Treatment Effect (SMD)	Modified I^2 (%)	Group-based CBT-I (SMD)	Individual-based CBT-I (SMD)
Sleep[§]	Post-Rx	Junquist et al. [25] & Vitiello et al. [33]	0.86 [0.57, 1.15]****	37%	0.51 [0.17, 0.86]*	1.28 [0.70, 1.86]***
	Follow-Up	Currie et al. [24]	0.40 [0.19, 0.61]**	18%	0.52 [0.09, 0.95]†	0.67 [0.30, 1.03]**
Pain	Post-Rx	N/A	N/A	N/A	0.23 [0.05, 0.41]†	0.14 [−0.09, 0.38]
	Follow-Up	Smith et al. [38]	0.26 [−0.01, 0.53]	44%	0.34 [0.10, 0.57]*	−0.13 [−0.47, 0.21]
Depressive Symptoms	Post-Rx	Jungquist et al. [25]	0.30 [−0.00, 0.60]‡	44%	0.16 [−0.09, 0.41]	1.09 [0.23, 1.94]†
	Follow-Up	N/A	N/A	N/A	0.01 [−0.24, 0.26]	N/A
Anxiety Symptoms	Post-Rx	N/A	N/A	N/A	0.04 [−0.29, 0.37]	0.37 [−0.04, 0.77]
	Follow-Up	N/A	N/A	N/A	−0.22 [−0.56, 0.11]	N/A
Fatigue	Post-Rx	Martinez et al. [26] & Lami [36]	1.49 [0.65, 2.33]**	0%	−0.28 [−1.33, 0.76]	1.49 [0.65, 2.33]**
	Follow-Up	N/A	N/A	N/A	N/A	N/A

[§] Global measures of sleep included the Insomnia Severity Index, Pittsburgh Sleep Quality Index, and Insomnia Symptom Questionnaire.
****p < 0.00001, ***p < 0.0001, **p < 0.001, *p < 0.01, †p < 0.05, ‡p = 0.05.

participants in the hybrid treatment with more severe baseline insomnia and pain had significant improvements in pain when compared with CBT-P alone at 18 mo [31]. This finding suggests that the addition of insomnia treatment to CBT-P may have an added benefit on pain in patients with more severe symptoms. Given the few number of studies, larger RCTs incorporating long follow-up periods are required to determine whether utilizing a hybrid protocol could effectively target both insomnia and pain.

Few studies have investigated the use of other non-pharmacological treatments for comorbid insomnia with chronic non-cancer pain. These interventions, such as Tai Ji Quan (a martial art) [72], hydrotherapy [73], massage-myofacial therapy [74], and manual therapy [75], have shown to improve pain and sleep quality in patients with fibromyalgia. Additionally, the effects of pain medications on sleep have been explored. Specifically, administering pregabalin led to significant improvements in pain and sleep compared with placebo in patients with fibromyalgia [76–80]. By improving pain levels, opioid therapy may also improve sleep. However, a recent systematic review and meta-analysis reported inconsistent and small effects of opioid therapy on subjective sleep quality, with the presence of excessive daytime sleepiness in patients with chronic non-cancer pain [81]. Given the small number and methodological quality of trials, further research is needed to evaluate the effects of alternative nonpharmacological and pharmacological treatments on both objective and subjective measures of sleep and pain.

We found a significant therapeutic effect on depressive symptoms at post-treatment (SMD = 0.44) [19,20,24–26,33,37,39]. Contrary to our findings, a previous meta-analysis did not report significant treatment effects on depressive symptoms in patients with chronic non-malignant pain, possibly due to insufficient power with only five studies included in their analysis [18]. In spite of individual trials reporting significant effects on anxiety symptoms [26] and fatigue [19,20,26,36], we did not observe treatment effects on anxiety symptoms or fatigue, although the impact on fatigue became significant when potential sources of heterogeneity were removed [26,36] and individual CBT-I [19,20] was analyzed separately. Given the limited number of studies examining the effectiveness of CBT-I on anxiety symptoms and fatigue in patients with chronic pain, further research in this area is warranted.

The overall quality of trials generally ranged from moderate to high with the exception of one study [35], although several trials reported small sample sizes and unclear allocation concealment procedures. Having an overall score of ≥25 on the Yates quality rating scale was associated with greater treatment effects on sleep at post-treatment. Most studies provided a detailed description of the CBT-I protocol and used robust inclusion criteria for chronic pain and insomnia diagnoses. Given that none of the studies reported blinding of both participants and researchers (outcome assessors and therapists), performance bias and expectation bias could have impacted findings. Therefore, the positive effect of CBT-I on insomnia may partly be a result of expectations that the treatment will improve their sleep over time. Additionally, most trials (92%) included in the meta-analysis reported a final follow-up at less than one year after baseline. Hence, whether CBT-I can elicit durable effects on sleep and pain remains uncertain.

The current study has several limitations. Publication bias was detected for post-treatment results on sleep, indicating that published results may be different from unpublished studies. Our search was also restricted to English-language and published studies only. Of the 12 RCTs included in the analyses, only two studies used double-blinded procedures, whereby participants were not told which of the interventions were active and blinded to the nature of the control interventions, assessors were blinded to group assignment, and interventionists were blinded to group assignment and the purpose of the control interventions [33,38]. Potential sources of heterogeneity across studies could be differences in chronic pain types or treatment protocols (e.g., components, delivery, and format). To address this limitation, guidelines outlining standardized methodological and CBT-I treatment procedures should be created and followed by future RCTs. Although sensitivity analyses were conducted to reduce heterogeneity, moderate heterogeneity was found for pain at follow-up (44%) and depressive symptoms at post-treatment (44%). Additionally, post-treatment effects on fatigue became significant upon removal of these studies, suggesting a possible introduction of bias and underpowered results. Indeed, the current meta-analysis comprised 12 RCTs only, nine of which had less than 100 participants [19,20,24–26,34,35,38,39]. Some of our analyses had less than

Multidimensional Pain Inventory; MPI-PS, Multidimensional Pain Inventory Pain Severity subscale; MPQ, McGill Pain Questionnaire; MPQ-SF-VAS; McGill Pain Questionnaire Short Form Visual Analogue Scale; MPQ-SF; McGill Pain Questionnaire Short Form; PSQI; Pittsburgh Sleep Quality Index; WOMAC Index; Western Ontario and McMaster Universities Osteoarthritis Index.

three studies per cell, such as the subgroup analyses on group- versus individual-based CBT-I, our post-hoc analysis of hybrid trials at follow-up, and effects on fatigue at follow-up. Including higher powered studies in future meta-analyses could reduce the likelihood of introducing bias when conducting sensitivity and subgroup analyses. Due to concerns of major heterogeneity in the technology and methodological procedures used to collect objective data (e.g., actigraphy), the current meta-analysis included subjectively reported outcomes only. However, patient-reported assessments are subject to recall bias and may not accurately reflect the patient's health. Other non-sleep-related outcomes, such as quality of life and physical functioning, should also be included in future trials to determine whether CBT-I can affect overall health.

Conclusion

This systematic review and meta-analysis found that CBT-I is effective for eliciting short- and long-term improvements in sleep, along with short-term improvements in pain and depressive symptoms in patients with comorbid insomnia and chronic non-malignant pain. Across 10 RCTs [19,20,24–26,33–36,38], we found a probability of 81% and 71% for having better sleep after CBT-I at post-treatment and final follow-up, respectively. The probability of having less pain after CBT-I at post-treatment and final follow-up was 58% and 57%, respectively. No treatment effects were found on anxiety symptoms or fatigue. Since insomnia is often reported as a comorbidity in patients with chronic pain [12], CBT-I could be used as the first-line of treatment in this population with fewer side effects than pharmacological therapies [82,83]. Additionally, future trials should incorporate larger sample sizes, components from CBT-P to actively target pain, self-help formats, and longer follow-up periods to determine whether CBT-I can elicit sustainable effects in patients with chronic pain.

Practice points

1. There is a high prevalence of insomnia among the chronic non-cancer pain population, and sleep is a stronger predictor of subsequent pain than vice versa.
2. CBT-I elicits immediate and long-term improvements in patient-reported sleep.
3. Short-term treatment effects are evident in other health outcome measures, including pain and depressive symptoms.

Research agenda

1. Larger and adequately powered randomized controlled trials are needed to examine the effectiveness of CBT-I on comorbid insomnia and chronic pain.
2. Longer follow-up periods are recommended to further investigate the long-term effects of CBT-I.
3. Further research is needed to determine whether hybrid interventions combining CBT-I and CBT-P can better address both insomnia and chronic pain symptoms.
4. Future studies should include objective measures of sleep and pain, along with non-sleep-related outcomes such as quality of life and physical functioning.

Conflicts of interest

MN reports the Academic Medical Organization Southwestern Ontario (AMOSO) opportunity fund, Alternative Fund Plan (AFP) Innovation fund and Lawson Internal Research fund. CAE reports National Institute for Health Research: Oxford Biomedical Research Centre; shareholder in Big Health. CMM reported research grant from CIHR, Fonds de recherche du Québec, Idorsia and Canopy Health, Consultant/Advisory Board for Eisai, Merck, Pear Therapeutics, Sunovion, Weight Watchers. FC reports research support from the Ontario Ministry of Health and Long-Term Care, University Health Network Foundation, Up-to-date royalties, consultant to Takeda Pharma and Masimo, STOP-Bang proprietary to University Health Network. JS, CP, PWHP, and ME did not report conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2021.101460.

References

[1] Covington EC, Mathews M. Chronic non malignant pain. In: Carrey WD, editor. Current clinical medicine. Philadelphia: Saunders Elsevier; 2009. p. 989–96.
[2] Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults — United States, 2016. MMWR Morb Mortal Wkly Rep 2018;67:1001–6.
[3] Cheatle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhingra L. Assessing and managing sleep disturbance in patients with chronic pain. Anesthesiol Clin 2016;34:279–93.
[4] Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. Sleep 2007;30(2):213–8.
[5] Tang NK, Wright KJ, Salkovskis PM. Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. J Sleep Res 2007;16(1):85–95.
[6] McCracken LM, Iverson GL. Disrupted sleep patterns and daily functioning in patients with chronic pain. Pain Res Manag 2002;7(2):75–9.
[7] Smith MT, Perlis ML, Smith MS, Giles DE, Carmody TP. Sleep quality and presleep arousal in chronic pain. J Behav Med 2000;23(1):1–13.
[8] Burgess HJ, Burns JW, Buvanendran A, Gupta R, Chont M, Kennedy M, et al. Associations between sleep disturbance and chronic pain intensity and function. Clin J Pain 2019;35(7):569–76.
[9] Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. J Pain 2013;14(12):1539–52.
[10] Robertson JA, Purple RJ, Cole P, Zaiwalla Z, Wulff K, Pattinson KT. Sleep disturbance in patients taking opioid medication for chronic back pain. Anaesthesia 2016;71(11):1296–307.
[11] Wei Y, Blanken TF, Van Someren EJ. Insomnia really hurts: effect of a bad night's sleep on pain increases with insomnia severity. Front Psychiatr 2018;9:377.
[12] Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev 2004;8(2):110–32.
[13] Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, et al. Sleep disturbances in chronic pain: neurobiology, assessment, and treatment in physical therapist Practice. Phys Ther 2018;98(5):325–35.
[14] Anderson KN. Insomnia and cognitive behavioural therapy-how to assess your patient and why it should be a standard part of care. J Thorac Dis 2018;10(Suppl 1):S94–102.

* The most important references are denoted by an asterisk.

[15] Finan PH, Buenaver LF, Runko VT, Smith MT. Cognitive-behavioral therapy for comorbid insomnia and chronic pain. Sleep Med Clin 2014;9(2):261–74.

[16] Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TD. Management of chronic insomnia disorder in adults; a clinical practice guideline from the American college of physicians. Ann Intern Med 2016;165:125–33.

[17] Bohra MH, Espie CA. Is cognitive behavioural therapy for insomnia effective in treating insomnia and pain in individuals with chronic non-malignant pain? Br J Pain 2013;7(3):138–51.

[18] Tang NK, Lereya ST, Boulton H, Miller MA, Wolke D, Cappuccio FP. Non-pharmacological treatments of insomnia for long-term painful conditions: a systematic review and meta-analysis of patient-reported outcomes in randomized controlled trials. Sleep 2015;38(11):1751–64.

*[19] Pigeon WR, Moynihan J, Matteson-Rusby S, Jungquist CR, Xia Y, Tu X, et al. Comparative effectiveness of CBT interventions for co-morbid chronic pain & insomnia: a pilot study. Behav Res Ther 2012;50(11):685–9.

*[20] Tang NK, Goodchild CE, Salkovskis PM. Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. Behav Res Ther 2012;50(12):814–21.

[21] Kim KM, Lee DH, Lee EJ, Roh YH, Kim WJ, Cho SJ, et al. Self-reported insomnia as a marker for anxiety and depression among migraineurs: a population-based cross-sectional study. Sci Rep 2019;9:19608.

[22] Li L, Wu C, Gan Y, Qu X, Lu Z. Insomnia and the risk of depression: a meta-analysis of prospective cohort studies. BMC Psychiatr 2016;16(1):375.

[23] Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep 2007;30(7):873–80.

*[24] Currie SR, Wilson KG, Pontefract AJ, deLaplante L. Cognitive-behavioral treatment of insomnia secondary to chronic pain. J Consult Clin Psychol 2000;68(3):407–16.

*[25] Jungquist CR, O'Brien C, Matteson-Rusby S, Smith MT, Pigeon WR, Xia Y, et al. The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. Sleep Med 2010;11(3):302–9.

*[26] Martínez MP, Miró E, Sánchez AI, Díaz-Piedra C, Cáliz R, Vlaeyen JW, et al. Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. J Behav Med 2014;37(4):683–97.

[27] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.

[28] Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[29] Yates SL, Morley S, Eccleston C, de C Williams AC. A scale for rating the quality of psychological trials for pain. Pain 2005;117(3):314–25.

[30] Graham N, Haines T, Goldsmith CH, Gross A, Burnie S, Shahzard U, et al. Reliability of 3 assessment tools used to evaluate randomized controlled trials for treatment of neck pain. Spine (Phila Pa 1976) 2012;37(6):515–22.

[31] McCurry SM, Shortreed SM, Von Korff M, Balderson BH, Baker LD, Rybarczyk BD, et al. Who benefits from CBT for insomnia in primary care? Important patient selection and trial design lessons from longitudinal results of the Lifestyles trial. Sleep 2014;37(2):299–308.

[32] Miró E, Lupiáñez J, Martínez MP, Sánchez AI, Díaz-Piedra C, Guzmán MA, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. J Health Psychol 2011;16(5):770–82.

*[33] Vitiello MV, McCurry SM, Shortreed SM, Balderson BH, Baker LD, Keefe FJ, et al. Cognitive-behavioral treatment for comorbid insomnia and osteoarthritis pain in primary care: the lifestyles randomized controlled trial. J Am Geriatr Soc 2013;61(6):947–56.

*[34] Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch Intern Med 2005;165(21):2527–35.

*[35] Heffner KL, France CR, Ashrafioun L, Quiñones M, Walsh P, Maloney MD, et al. Clinical pain-related outcomes and inflammatory cytokine response to pain following insomnia improvement in adults with knee osteoarthritis. Clin J Pain 2018;34(12):1133–40.

*[36] Lami MJ, Martínez MP, Miro E, Sanchez AI, Prados G, Caliz R, et al. Efficacy of combined cognitive-behavioral therapy for insomnia and pain in patients with fibromyalgia: a randomized controlled trial. Cognit Ther Res 2018;42(1):63–79.

*[37] McCrae CS, Williams J, Roditi D, Anderson R, Mundt JM, Miller MB, et al. Cognitive behavioral treatments for insomnia and pain in adults with co-morbid chronic insomnia and fibromyalgia: clinical outcomes from the SPIN randomized controlled trial. Sleep 2019;42(3):zsy234.

*[38] Smith MT, Finan PH, Buenaver LF, Robinson M, Haque U, Quain A, et al. Cognitive-behavioral therapy for insomnia in knee osteoarthritis: a randomized, double-blind, active placebo-controlled clinical trial. Arthritis Rheum 2015;67(5):1221–33.

*[39] Vitiello MV, Rybarczyk B, Von Korff M, Stepanski EJ. Cognitive behavioral therapy for insomnia improves sleep and decreases pain in older adults with co-morbid insomnia and osteoarthritis. J Clin Sleep Med 2009;5(4):355–62.

[40] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum 1990;33(2):160–72.

[41] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3rd ed. Washington: American Psychiatric Association; 1980.

[42] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: American Psychiatric Association; 1994.

[43] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington: American Psychiatric Association; 2000. text revision.

[44] Edinger JD, Bonnet MH, Bootzin RR, Doghramji K, Dorsey CM, Espie CA, et al. Derivation of research diagnostic criteria for insomnia: report of an American academy of sleep medicine work group. Sleep 2004;27(8):1567–96.

[45] Morin CM. Insomnia: psychological assessment and management. New York: Guilford Press; 1993.

[46] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28(2):193–213.

[47] Spielman AJ, Saskin P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. Sleep 1987;10(1):45–56.

[48] Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1(3):277–99.

[49] Melzack R. The short-form McGill pain questionnaire. Pain 1987;30(2):191–7.

[50] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatr 1961;4:561–71.

[51] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17(1):37–49.

[52] Dragioti E, Levin LÅ, Bernfort L, Larsson B, Gerdle B. Insomnia severity and its relationship with demographics, pain features, anxiety, and depression in older adults with and without pain: cross-sectional population-based results from the PainS 65+ cohort. Ann Gen Psychiatr 2017;16:15.

[53] Kim SH, Lee DH, Yoon KB, An JR, Yoon DM. Factors associated with increased risk for clinical insomnia in patients with chronic neck pain. Pain Physician 2015;18(6):593–8.

[54] Nicassio PM, Moxham EG, Schuman CE, Gevirtz RN. The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. Pain 2002;100(3):271–9.

[55] Wang HY, Fu TS, Hsu SC, Hung CI. Association of depression with sleep quality might be greater than that of pain intensity among outpatients with chronic low back pain. Neuropsychiatric Dis Treat 2016;12:1993–8.

[56] Espie CA. Stepped care": a health technology solution for delivering cognitive behavioral therapy as a first line insomnia treatment. Sleep 2009;32(12):1549–58.

[57] Koffel EA, Koffel JB, Gehrman PR. A meta-analysis of group cognitive behavioral therapy for insomnia. Sleep Med Rev 2015;19:6–16.

[58] Geiger-Brown JM, Rogers VE, Liu W, Ludeman EM, Downton KD, Diaz-Abad M. Cognitive behavioral therapy in persons with comorbid insomnia: a meta-analysis. Sleep Med Rev 2015;23:54–67.

[59] Arnedt JT, Conroy DA, Mooney A, Furgal A, Sen A, Eisenberg D. Telemedicine versus face-to-face delivery of cognitive behavioral therapy for insomnia: a randomized controlled non-inferiority trial. Sleep 2020:zsaa136 [published online ahead of print, 2020 Jul 13].

[60] Ho FY, Chung KF, Yeung WF, Ng TH, Kwan KS, Yung KP, et al. Self-help cognitive-behavioral therapy for insomnia: a meta-analysis of randomized controlled trials. Sleep Med Rev 2015;19:17–28.

[61] McCurry SM, Guthrie KA, Morin CM, Woods NF, Landis CA, Ensrud KE, et al. Telephone-based cognitive behavioral therapy for insomnia in perimenopausal and postmenopausal women with vasomotor symptoms: a MsFLASH randomized clinical trial. JAMA Intern Med 2016;176(7):913–20.

[62] Zachariae R, Lyby MS, Ritterband LM, O'Toole MS. Efficacy of internet-delivered cognitive-behavioral therapy for insomnia–a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2016;30:1–10.

[63] McCurry SM, Von Korff M, Morin CM, Cunningham A, Pike KC, Thakral M, et al. Telephone interventions for co-morbid insomnia and osteoarthritis pain: the OsteoArthritis and Therapy for Sleep (OATS) randomized trial design. Contemp Clin Trials 2019;87:105851.

[64] Cheng SK, Dizon J. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. Psychother Psychosom 2012;81(4):206–16.

[65] Knoerl R, Lavoie Smith EM, Weisberg J. Chronic pain and cognitive behavioral therapy: an integrative review. West J Nurs Res 2016;38(5):596–628.

[66] Afolalu EF, Ramlee F, Tang NKY. Effects of sleep changes on pain-related health outcomes in the general population: a systematic review of longitudinal studies with exploratory meta-analysis. Sleep Med Rev 2018;39:82–97.

[67] Ødegård SS, Sand T, Engstrøm M, Zwart JA, Hagen K. The impact of headache and chronic musculoskeletal complaints on the risk of insomnia: longitudinal data from the Nord-Trøndelag health study. J Headache Pain 2013;14(1):24.

[68] Tang NK, McBeth J, Jordan KP, Blagojevic-Bucknall M, Croft P, Wilkie R. Impact of musculoskeletal pain on insomnia onset: a prospective cohort study. Rheumatology (Oxford) 2015;54(2):248–56.

[69] Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems [published correction appears in Sleep. Sleep 2007;30(2):213–8. 2007 Jul 1;30(7):table of contents].

[70] MacDonald S, Linton SJ, Jansson-Frojmark M. Avoidant safety behaviors and catastrophizing: shared cognitive-behavioral processes and consequences in co-morbid pain and sleep disorders. Int J Behav Med 2008;15(3):201–10.
[71] Tang NKY. Cognitive behavioural therapy in pain and psychological disorders: towards a hybrid future. Prog Neuro-Psychopharmacol Biol Psychiatry 2018;87(Pt B):281–9. https://doi.org/10.1016/j.pnpbp.2017.02.023.
[72] Maddali Bongi S, Paoletti G, Calà M, Del Rosso A, El Aoufy K, Mikhaylova S. Efficacy of rehabilitation with Tai Ji quan in an Italian cohort of patients with fibromyalgia syndrome. Compl Ther Clin Pract 2016;24:109–15.
[73] Vitorino DF, Carvalho LB, Prado GF. Hydrotherapy and conventional physiotherapy improve total sleep time and quality of life of fibromyalgia patients: randomized clinical trial. Sleep Med 2006;7(3):293–6.
[74] Castro-Sánchez AM, Matarán-Peñarrocha GA, Granero-Molina J, Aguilera-Manrique G, Quesada-Rubio JM, Moreno-Lorenzo C. Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia. Evid Based Complement Alternat Med 2011;2011:561753.
[75] Castro-Sánchez AM, Aguilar-Ferrándiz ME, Matarán-Peñarrocha GA, Sánchez-Joya Mdel M, Arroyo-Morales M, Fernández-de-las-Peñas C. Short-term effects of a manual therapy protocol on pain, physical function, quality of sleep, depressive symptoms, and pressure sensitivity in women and men with fibromyalgia syndrome: a randomized controlled trial. Clin J Pain 2014;30(7):589–97.
[76] Arnold LM, Russell IJ, Diri EW, Duan R, Young Jr JP, Sharma U, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. J Pain 2008;9(9):792–805.
[77] Crofford LJ, Rowbotham MC, Mease PJ, Russell IJ, Dworkin RH, Corbin AE, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52(4):1264–73.
[78] Mease PJ, Russell IJ, Arnold LM, Florian H, Young Jr JP, Martin SA, et al. A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008;35(3):502–14.
[79] Pauer L, Winkelmann A, Arsenault P, Jespersen A, Whelan L, Atkinson G, et al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. J Rheumatol 2011;38(12):2643–52.
[80] Roth T, Lankford DA, Bhadra P, Whalen E, Resnick EM. Effect of pregabalin on sleep in patients with fibromyalgia and sleep maintenance disturbance: a randomized, placebo-controlled, 2-way crossover polysomnography study. Arthritis Care Res 2012;64(4):597–606.
[81] Tang NKY, Stella MT, Banks PDW, Sandhu HK, Berna C. The effect of opioid therapy on sleep quality in patients with chronic non-malignant pain: a systematic review and exploratory meta-analysis. Sleep Med Rev 2019;45:105–26.
[82] Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. BMC Fam Pract 2012;13:40.
[83] Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4(5):487–504.