pii: sp-00773-14

Nonpharmacological Treatments of Insomnia for Long-Term Painful Conditions: A Systematic Review and Meta-analysis of Patient-Reported Outcomes in Randomized Controlled Trials

Nicole K.Y. Tang, DPhil[1]; S. Tanya Lereya, PhD[1]; Hayley Boulton, PhD[1]; Michelle A. Miller, PhD[2]; Dieter Wolke, PhD[1,2]; Francesco P. Cappuccio, MD, FRCP[2]

[1]Department of Psychology, University of Warwick, Coventry, UK; [2]Warwick Medical School, University of Warwick, Coventry, UK

Study Objectives: Insomnia is a debilitating comorbidity of chronic pain. This study evaluated the effect of nonpharmacological sleep treatments on patient-reported sleep quality, pain, and well-being in people with long-term cancer and non-cancer (e.g., back pain, arthritis, fibromyalgia) pain conditions.

Design: We systematically searched Cochrane CENTRAL, MEDLINE, Embase, and PsychINFO for relevant studies. Search period was set to inception of these databases to March 2014. Studies were included if they were: original randomized controlled trials (RCTs); testing a nonpharmacological intervention; that targets sleep; in adults; with painful health conditions; that has a control group; includes a measure of sleep quality; and at least one other health and well-being outcome.

Measurement and Findings: Means and standard deviations of sleep quality, pain, fatigue, depression, anxiety, physical and psychological functioning were extracted for the sleep treatment and control groups at baseline, posttreatment and final follow-up. Methodological details concerning the treatment, participants, and study design were abstracted to guide heterogeneity and subgroup analyses. Eleven RCTs involving 1,066 participants (mean age 45–61 years) met the criteria for the meta-analysis. There was no systematic evidence of publication bias. Nonpharmacological sleep treatments in chronic pain patients were associated with a large improvement in sleep quality (standardized mean difference = 0.78, 95% Confidence Interval [0.42, 1.13]; P < 0.001), small reduction in pain (0.18 [0, 0.36] P < 0.05), and moderate improvement in fatigue (0.38 [0.08, 0.69]; P < 0.01) at posttreatment. The effects on sleep quality and fatigue were maintained at follow-up (up to 1 year) when a moderate reduction in depression (0.31, [0.09, 0.53]; P < 0.01) was also observed. Both cancer and non-cancer pain patients benefited from nonpharmacological sleep treatments. Face-to-face treatments achieved better outcomes than those delivered over the phone/internet.

Conclusions: Although the body of evidence was small, nonpharmacological sleep interventions may represent a fruitful avenue for optimizing treatment outcomes in patients with chronic pain.

Registration: (PROSPERO registration: CRD42013004131).

Keywords: insomnia, chronic pain, meta-analysis, nonpharmacological treatment, health

Citation: Tang NK, Lereya T, Boulton H, Miller MA, Wolke D, Cappuccio FP. Nonpharmacological 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): 1751-1764

INTRODUCTION

Poor sleep is a potential cause of ill-health. Self-reported short and long habitual sleep duration, difficulties initiating or maintaining sleep, non-restorative sleep, and the use of hypnotic drugs are significant predictors of obesity, diabetes, widespread pain, stroke, coronary heart disease (CHD), and even mortality.[1–6] Insomnia also increases the risk of subsequent onset of depression, anxiety disorders and substance misuse in otherwise healthy individuals.[7–10] These findings, assuming they reflect causality, highlight sleep as a plausible therapeutic target for preventing a range of long-term conditions.

Insomnia is a major problem to many people living with chronic pain that lasts longer than 3–6 months.[11] Chronic pain has been ranked the top cause of quality-adjusted life-year loss in primary care, ahead of recognized sources of burden of disease such as depression, anxiety disorders, diabetes, respiratory conditions, high blood pressure and CHD.[12] It is estimated that 50% to 90% of chronic pain patients report insomnia of a severity that warrants clinical attention.[13–16] In experimental studies, the introduction of sleep disruption can trigger pro-inflammatory responses, reduce endogenous pain inhibitory control, amplify pain experience, lower pain tolerance, and increase somatic symptoms.[17–20] These findings are in line with the idea of a reciprocal, rather than unidirectional, relationship between sleep and pain.[21–25] Recently, there has been a surge of interest in applying established nonpharmacological sleep interventions to treat chronic pain patients with comorbid insomnia. At odds with the hypothesized reciprocal relationship, results have been inconsistent. While some studies observed no change in pain post-intervention,[26–29] others found a significant reduction in pain intensity after sleep improvement.[30–32] It remains unclear whether better sleep could lead to less pain and better health and well-being.

The current meta-analysis aimed to evaluate the efficacy of non-pharmacological sleep interventions for people with long-term cancer and non-cancer painful conditions. We were interested in the effect of these interventions on sleep and their broader impact on health and well-being as indicated by pain, fatigue, depression, anxiety, physical and psychosocial functioning. We restricted our evaluation to nonpharmacological sleep interventions only, because pharmacological sleep interventions were not recommended for the protracted type of insomnia experienced by patients with chronic pain.[33] Based on the similarities in presentation and underpinning mechanisms between primary and pain-related insomnia,[34,35] it was hypothesized that

Submitted for publication December, 2014
Submitted in final revised form March, 2015
Accepted for publication March, 2015
Address correspondence to: Nicole KY Tang, Department of Psychology, University of Warwick, Coventry, CV4 7AL, UK; Tel: +44 (0)2476 150556; Email: n.tang@warwick.ac.uk

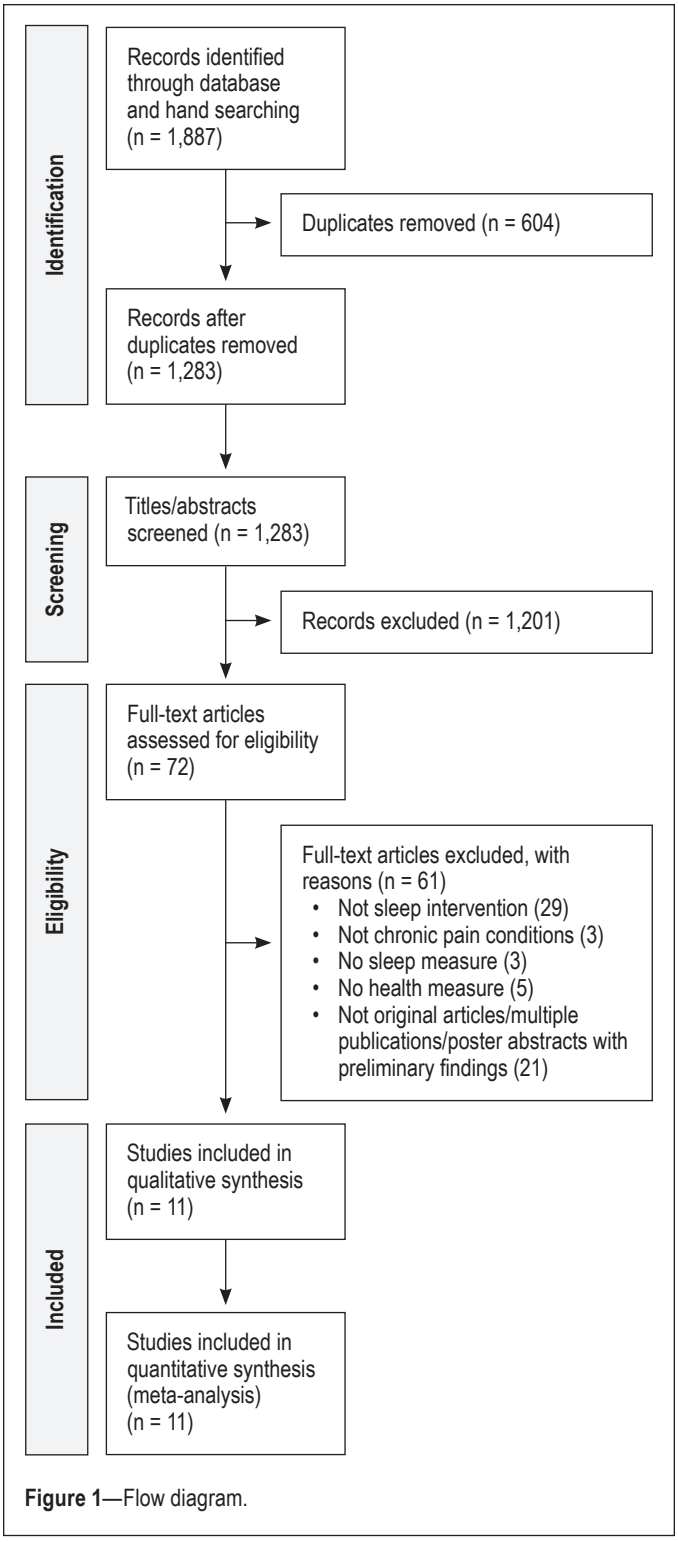

Figure 1—Flow diagram.

nonpharmacological sleep interventions would have a beneficial impact on sleep. However, the meta-analysis was exploratory with regards to the effect of these interventions on the aforementioned health and well-being outcomes.

METHODS

Data Sources and Searches

Our data sources were original randomized controlled trials (RCTs) testing the utility of nonpharmacological treatments for insomnia in adults with long-term painful conditions. To identify these, we performed systematic searches in 4 electronic databases; Cochrane CENTRAL, MEDLINE, Embase, and PsychINFO. The search duration was between the inception of each database and March 2014. No language restriction was applied. Abstracts/articles written in foreign languages were translated for review.

Search terms used (Appendix, supplemental material) were decided *a priori* by the review team after consulting published systematic reviews/meta-analyses[36,37] and conducting a series of pilot searches. A methodological filter (e.g., random* in Trials) was used in combination with search keywords that reflected the treatment approach (e.g., nonpharma*, psychologic*), treatment content (e.g., sleep, insomnia) and population (e.g., chronic next pain*, cancer, musculo*, arthritis*) of interest. We took a transdiagnostic approach to amalgamate a range of malignant and non-malignant conditions presented with chronic pain.[38] This we hoped would reflect the increasing application of nonpharmacological sleep interventions beyond primary insomnia[39] and offer an opportunity to compare the effectiveness of these treatments between diagnostic subgroups.

The searches and subsequent screening were independently carried out by two of the authors (STL and HB). Disagreements between reviewers were resolved via discussion with the review team. Reference lists of included studies and relevant review articles were hand-searched to ensure comprehensive coverage. Gray literature (e.g., conference abstracts and PhD theses) was also consulted to reduce the risk of publication bias.

Study Selection

Figure 1 depicts the searches and screening process. The searches yielded a total of 1,887 records. After 604 duplicates between databases were removed, 1,283 titles and abstracts were screened. In the instance of foreign language, abstracts were translated into English for a judgment to be made.[40] Seventy-two articles were selected for full-text screening, which was aided with a checklist developed by NKYT and MAM according to the inclusion criteria: original RCT; testing a nonpharmacological intervention; that targets sleep; in adults (aged 18 years); with painful health conditions (e.g., musculoskeletal pain, arthritis, fibromyalgia, headache, cancer); that has a control group; includes an outcome measure of sleep; and at least one other health and well-being outcome.

A broad definition of nonpharmacological treatments for insomnia was adopted. These treatments might include the sole or combined use of components of cognitive behavior therapy for insomnia (CBT-I). Common components of CBT-I include psychoeducation, sleep hygiene, stimulus control therapy, sleep restriction therapy, sleep scheduling, relaxation, paradoxical intention, imagery, and cognitive therapy.[33,41] Studies testing the utility of physiotherapies, exercise, yoga, qigong, mindfulness meditation, massage, acupuncture, hormone therapy, and hypnosis were included if the interventions being evaluated were designed to address insomnia specifically. If multiple publications were available for the same trial, only the article reporting the primary analysis with the most relevant information to the current meta-analysis was included.[32,42–44] We did not automatically exclude non-inferiority trials from the meta-analysis if nonpharmacological sleep interventions

were tested as the standard treatment control against which a novel treatment demonstrated non-inferiority.[45]

Following the full-text screening, 61 studies did not meet criteria for inclusion and 11 studies were selected for data extraction. High inter-rater agreement was noted for both the title/abstract ($\kappa = 0.90$, $P < 0.001$) and the full-text screens ($\kappa = 1.00$, $P < 0.001$).

Data Extraction and Quality Assessment

Data extraction was performed in duplicate to counteract human errors and individual biases (HB & STL). In addition to extracting relevant data on sleep, health, and well-being outcomes, information was gathered from individual studies to compose a study characteristics table (Table 1) which incorporated methodological details about the design of the trials (sample size, participants, number of arms), treatments tested (content, duration, method of delivery), outcome measures used, whether intention-to-treat analysis was applied, and their quality ratings. When data were not available in the published report, authors were contacted to provide information. The data extraction sheets were checked by the review team and differences between reviewers were resolved by discussion.

For the meta-analysis, means and standard deviations of relevant outcome measures were extracted for the sleep treatment and control group at baseline, posttreatment (i.e., immediately on completion of the sleep/control intervention), and the final follow-up (due to variability in assessment timing). For studies that used multiple measures to assess the same outcome, the most prevalent measure used across the final 11 studies was used to maximize comparability of the findings.

We assessed the risk of bias quantitatively using the quality rating scale developed by Yates and colleagues[46] and qualitatively following the Cochrane guidance.[47] The quality rating scale was designed to assess RCTs of nonpharmacological treatment for the quality of the treatment and the design and reporting of the trials. The scale has shown face, content, and construct validity, and good inter-rater reliability.[46] The overall score of the scale ranges from 0 to 35 with higher scores indicating better quality. In the validation studies involving 17 RCTs of nonpharmacological treatments for chronic pain being assessed by two expert reviewers, the mean total scores were 22.70 (SD 1.95) for "excellent," 18.71 (SD 2.25) for "average" and 12.10 (SD 3.17) for "poor" trials.[46] Of the 5 suggested Cochrane "risk of bias" categories,[47] we included random sequence generation (selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). We excluded the option of "blinding participants and personnel" because, during the delivery of most nonpharmacological treatments, neither therapists nor patients can be (sufficiently) blinded to the type of treatment they deliver or receive.

Data Synthesis and Analysis

Comparisons were made between the "sleep treatment" and "control" groups with reference to the change from baseline at posttreatment and at follow-up for each of the outcome measures. Changes were calculated such that a positive difference represents an improvement, a negative difference a deterioration. Since different measures were used to assess the same outcome in different studies, the change scores were transformed into z scores to reduce heterogeneity and enhance comparability using the standard formula:

$$z = \frac{x - \bar{x}}{s}$$

where x = pretreatment − posttreatment change, $\bar{x}$ = mean change of all included studies, and s = pooled standard deviation. Standardized mean differences (SMD) between the effect of treatment and control were then estimated using a random effect model.

For each outcome measure, data from all trials were entered into a funnel plot. Asymmetry of the plot was visually examined to detect overt publication bias. None of the analyses demonstrated overt asymmetry that required follow-ups with Egger's regression test. Statistical heterogeneity among the included studies was assessed using the χ^2 test and the I^2 statistic, along with visual inspection of the forest plot. Comparisons with significant heterogeneity were followed up by a sensitivity analysis in which one study was omitted at a time to identify the possible source of heterogeneity; the study that resulted in the largest drop in heterogeneity was removed. If dropping the first study did not sufficiently reduce heterogeneity to a non-significant level, a second study was then removed. Subgroup analyses were also carried out to examine possible sources of heterogeneity attributable to the study characteristics. Two exploratory subgroup analyses were defined *a priori* to compare the effect of sleep treatment between those with cancer pain and those with non-cancer pain patients, and between those with an intervention delivered face-to-face or using the phone or internet. The former subgroup analysis should provide insights into the applicability of nonpharmacological interventions for sleep across patients with malignant and non-malignant pain, while the latter should show if the effect of nonpharmacological sleep interventions varied by treatment delivery method. The diverse components of the treatment packages precluded any subgroup analysis by type of treatment for the identification of active treatment ingredients.

All statistical analyses were performed using RevMan 5.

RESULTS

Characteristics of the Included RCTs

A total of 11 RCTs involving 1,066 participants (female: 55% to 100%; mean age: 45–61 years) from 4 different countries (Canada = 3, Spain = 2, UK = 1, US = 5) provided data for the meta-analysis (Table 1).

Five of the RCTs tested the effect of nonpharmacological sleep treatments in patients with non-cancer chronic pain; 2 used a mixed variety of chronic pain patients (diagnosis confirmed by physicians),[26,28] while the other 3 involved fibromyalgia patients meeting the American College of Rheumatology criteria only.[27,29,48,49] Six of the RCTs tested the effect in cancer survivors; 2 of which comprised 100% breast cancer survivors,[42,50] while 4 involved survivors of different types of cancer (e.g., lung, lymphoma ovarian, prostate, colorectal and gynecological) in addition to a majority of breast cancer patients.[45,51–53]

Table 1—Study characteristics.

		Author, Publication Year and Country of Implementation			
		Currie et al. (2000) Canada	**Edinger et al. (2005) USA**	**Savard et al. (2005) Canada**	**Espie et al. (2008) UK**
Final Sample	N	60	47	57	150
	Age, mean	45.0	48.6	54.05	61
	Female %	55	96	100	69
	Type of pain	Chronic pain: back pain (72%), neck pain (20%), lower limbs pain (5%), pelvic pain (3%) Diagnosis confirmed by specialist in physical medicine	Fibromyalgia (100%) ACR criteria; Diagnosis confirmed by board-certified rheumatologist	Breast cancer (100%) Pts had completed radiotherapy & chemotherapy for Stage 1-III cancer ≥ 1 m prior to study	Cancer: breast (58%), prostate (23%), colorectal (16%), gynaecological (3%) Pts had completed radiotherapy & chemotherapy ≥ 1 m with no further anticancer treatment planned
	Insomnia diagnosis	DSM-IV	DSM-III-R + sleep diary + PSG	DSM-IV (> 30 min SOL/ WASO; SE < 85%; frequency ≥ 3 npw; duration > 6 m; daytime impairment) + PSG	DSM-IV (> 30 min SOL/ WASO; frequency ≥ 3 npw; duration ≥ 3 m; daytime impairment) + PSQI > 5
RCT	Number of arms	Two arms: CBT-I vs. WLC	Three arms: CBT-I vs. SH vs. TAU	Two arms: CBT-I vs. WLC	Two arms: CBT-I vs. TAU
	Treatment components	CBT-I: Basic education regarding sleep and the causes of chronic insomnia; Sleep restriction; Stimulus control; Relaxation training; Sleep hygiene; Cognitive therapy. WLC: Participants completed a sleep diary for 7 further weeks and received weekly phone calls (limited to 10 min) designed to encourage adherence.	CBT-I: Misconceptions about sleep needs were addressed (via audiocassette); Stimulus control instructions; Sleep restriction SH: Participants received generic sleep education (via audiocassette) and advice on sleep hygiene (in both verbal and written forms). Usual care: Ongoing medical care, plus weekly meeting with a study coordinator to submit sleep log, actigraphy data and completed questionnaires.	CBT-I: Stimulus control; Sleep restriction; Cognitive restructuring; Sleep hygiene; Fatigue and stress management. WLC: Following an 8 week wait period, participants received the same treatment.	CBT-I: Stimulus control; Sleep restriction; Cognitive therapy strategies. TAU: Normal clinical practice was received (e.g., appointments with physicians, prescriptions)
	Dose & Duration	7 weekly sessions (120 min)	6 weekly sessions (1st lasted 45–50 min and subsequent ones 15–30 min).	8 weekly sessions (~90 min)	5 weekly sessions (50 min)
	Delivery	Medium: Face-to-face session Format: Group (5 to 7 individuals) Manual: Yes Therapist(s): 2x Doctoral students or interns in clinical psychology	Medium: Face-to-face session Format: Individual (1:1) Manual: Yes Therapist(s): Licenced clinical psychologists	Medium: Face-to-face session Format: Group (4–6 individuals) Manual: Yes Therapist(s): An experienced masters-level psychologist	Medium: Face-to-face session Format: Group (4–6 individuals) Manual: Yes Therapist(s): Trained oncology nurses
Key Assessment Measures & Timing	Sleep	PSQI	ISQ	ISI**	SE
	Pain	MPI-PS	MPQ	–	–
	Fatigue	–	–	MFI	FSI
	Depression	BDI	–	HADS-D	HADS-D
	Anxiety	–	–	HADS-A	HADS-A
	Physical functioning	–	–	–	FACT-P
	Psychosocial functioning	–	SF-36-M	–	FACT-E
	Assessment points	Baseline, posttreatment, 3 months follow-up	Baseline, posttreatment, 6 month follow-up	Baseline, posttreatment, 3, 6, and 12 month follow-up	Baseline, posttreatment, 3 months follow-up
Missing Data	Intent-to-treat analysis	Yes	Yes	Yes	Yes
Quality Rating	Treatment quality	9	6.5	7	8
	Methodology	15	18.5	18.5	22
	Overall	24	25	25.5	30

Table 1 continues on the following page

Table 1 (*continued*)—Study characteristics.

		Author, Publication Year and Country of Implementation			
		Berger et al. (2009) USA	**Barsevick et al. (2010) USA**	**Jungquist et al. (2010) USA**	**Miro et al. (2011) Spain**
Final Sample	N	219	276	28	31
	Age, mean	51.57* (BT); 52.86* (Control)	53.97	49.1	46.45
	Female %	100	83	82	100
	Type of pain	Breast cancer (100%) Pts with initial diagnosis of stage I-IIIA cancer at least 48 hr before receiving adjuvant chemotherapy	Cancer: breast (55%), lung (17%), lymphoma (8%), and ovarian (6%) Pts were beginning a new chemotherapy regimen with any prior treatment completed ≥ 1 m previously	Chronic pain: lower back (64 %), neck (32%), and thoracic spinal level (4%) Diagnosis confirmed by full physical examination, urinalysis, bloodwork and neuropsychiatric interview; Pts were on stable pain treatment	Fibromyalgia (100%) ACR criteria; Pts were referrals from hospital rheumatology and pain services; Diagnosis confirmed by medical examination
	Insomnia diagnosis	Did not use diagnostic criteria; Pts' baseline mean PSQI score was > 5; 20% of the pts were on sleep medication at baseline;	Did not use diagnostic criteria; Pts' baseline mean PSQI score was between 7.83 and 8.01	Insomnia criteria (> 30 min SOL or WASO, frequency 3 npw, duration > 6 m)+ sleep diary + PSG	DSM-IV + interview + questionnaire + neuropsychological test + PSG
RCT	Number of arms	Two arms: BT vs. Healthy eating control	Two arms: Energy and Sleep Enhancement (EASE, treatment) vs. Nutrition control	Two arms: CBT-I vs. contact control	Two arms: CBT vs., SH
	Treatment components	BT: Stimulus control; Modified sleep restriction; Relaxation therapy; Sleep hygiene counselling. Healthy eating control: A new healthy eating topic was discussed and general support was provided.	EASE: Provision of information about symptoms; Advice on sleep enhancement and energy conservation strategies. Nutrition control: Provision of information about nutrition and a healthy diet.	CBT-I: Sleep restriction therapy; Stimulus control instructions; Sleep hygiene Cognitive therapy. Contact control: Weekly meetings (interrogative review) with the nurse therapist (with the duration comparable to that of the treatment group).	CBT: Information on the relationship between sleep and Fibromyalgia; Sleep hygiene; Sleep restriction; Stimulus control; Relaxation training; Cognitive therapy; Relapses prevention. SH: Considered sleep hygiene rules and environmental and lifestyle factors.
	Dose & Duration	1 appointment to devise a BT plan (90 min) + 4–8 additional appointments after each chemotherapy session to revise the BT plan (30 min) + 4–8 bolster sessions 7–9 days after each revision to reinforce the BT plan (15 min)	3 sessions conducted in the 2nd, 3rd and 4th week following CTX treatment (total mean duration = 69 min)	8 weekly sessions (30–90 min)	6 weekly sessions (90 min)
	Delivery	Medium: Face-to-face session Format: Individual (1:1) Manual: NR Therapist(s): Trained research nurses	Medium: Telephone Format: Individual (1:1) Manual: Yes Therapist(s): Trained oncology nurses	Medium: Face-to-face session Format: Individual (1:1) Manual: Yes Therapist(s): a Masters-level trained nurse	Medium: Face-to-face session Format: Group (5 to 6 individuals) Manual: Yes Therapist(s): CBT experts
Key Assessment Measures & Timing	Sleep	PSQI	PSQI	ISI	PSQI
	Pain	–¶	BPI	MPI-PS	MPQ
	Fatigue	PFS	GFS	–§	–
	Depression	HADS-D	POMS-D	BDI	HADS-D
	Anxiety	HADS-A	–	–	HADS-A
	Physical functioning	–	SF-12-P	–	–
	Psychosocial functioning	–	SF-12-M	–	–
	Assessment points	Baseline, posttreatment	Baseline, posttreatment	Baseline, posttreatment	Baseline, posttreatment
Missing Data	Intent-to-treat analysis	Yes	Yes	Yes	NR
Quality Rating	Treatment	5.5	8	8	8
	Methodology	19.5	19	17	17
	Overall	25	27	25	25

Table 1 continues on the following page

Table 1 (*continued*)—Study characteristics.

		Author, Publication Year and Country of Implementation		
		Ritterband et al. (2012) USA	**Martinez et al. (2013) Spain**	**Garland et al. (2014) Canada**
Final Sample	N	28	59	111
	Age Mean	56.7	47.58	58.89
	Female %	86	100	72
	Type of pain	Cancer: breast (64%), other (36%) Pts were recruited from a cancer centre and had completed active treatment (radiation, chemotherapy or surgery) ≥ 1m	Fibromyalgia (100%) ACR criteria (duration: > 6m); Pts were referrals from hospital rheumatology and pain services	Cancer: breast (48%), prostate (11%), blood/lymph (10%), genitourinary (10), colon (6%), head & neck (8%), lung (6%) and skin (2%) Pts were recruited from a tertiary cancer centre and had completed chemotherapy or radiation treatments ≥ 1 m
	Insomnia diagnosis	DSM-IV-TR (frequency: ≥ 3 npw; duration: ≥ 6 m; daytime consequences; ≤ 6.5 h TST)	DSM-IV-TR + sleep diary + interview + neuropsychological test + PSG	DSM-IV-TR (> 30 min SOL/WASO; < 85% SE; frequency ≥ 3 npw; duration ≥ 1 m; impairment in functioning)
RCT	Number of arms	Two arms: SHUTi (online CBT-I) vs., WLC	Two arms: CBT-I vs. SH	Two arms: CBT-I vs. MBSR
	Treatment components	SHUTi: Sleep restriction; Stimulus control; Sleep hygiene education; Thoughts restructuring; Problem prevention. WLC: Received access to the SHUTi program at the end of the study.	CBT-I: Information on the relationship between sleep and Fibromyalgia; Sleep hygiene; Sleep restriction; Stimulus control; Relaxation training; Cognitive therapy; Relapses prevention. SH: Considered sleep hygiene rules and environmental and lifestyle factors.	CBT-I: Stimulus control, sleep restriction, cognitive therapy and relaxation training. MBSR: Psychoeducation on stress and health, meditation, yoga, mindfulness training.
	Dose & Duration	9-week access to the 6-week program (45–60 min each of the 6 cores of the program)	6 weekly sessions (90 min)	8 weekly sessions (90 min)
	Delivery	Medium: Internet	Medium: Face-to-face session Format: Group (5 to 6 individuals) Manual: Yes Therapist(s): experienced therapists	Medium: Face-to-face session Format: Group (6 to 10 individuals) Manual: Yes Therapist(s): a doctoral student in clinical psychology
Key Assessment Measures & Timing	Sleep	ISI	PSQI	PSQI[Ω]
	Pain	–[‡]	MPQ-VAS	–
	Fatigue	MFSI-SF	MFI	–
	Depression	HADS-D	SCL-90-R-D	POMS-D
	Anxiety	HADS-A	SCL-90-R-A	POMS-A
	Physical functioning	SF-12-P	–	–
	Psychosocial functioning	SF-12-M	–	–
	Assessment points	Baseline, posttreatment	Baseline, posttreatment, 3- and 6-month follow-up	Baseline, posttreatment, 3-month follow-up
Missing Data	Intent-to-treat analysis	NR	NR	Yes
Quality Rating	Treatment	3.5	7	7
	Methodology	18	20	23.5
	Overall	21.5	27	30

*Median was reported. **Patient version used. [¶]Pain was measured with an item in the Symptom Experience Scale but not reported individually as an outcome. [§]MFI scores were not reported. [‡]Pain was measured as one of the eight domains that constituted the SF-12. Ω = Both PSQI and ISI scores were available. PSQI score was used in the analysis to enhance comparability between findings of studies. NR, not reported; Pt(s), patient(s); DSM-III-R, American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorder (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); PSG, polysomnography; SOL, sleep onset latency; WASO, wake after sleep onset; TST, total sleep time; SE, sleep efficiency; ACR criteria, American College of Rheumatology criteria for the diagnosis of fibromyalgia; CBT, cognitive behavior therapy; CBT-I, cognitive behavior therapy for insomnia; WLC, waitlist control; TAU, treatment as usual; SH, sleep hygiene; BT, behavioral therapy; SHUTi, Sleep Healthy Using the Internet; MBST, mindfulness-based stress reduction; PSQI, Pittsburgh Sleep Quality Index; MPI-PS, Multidimensional Pain Inventory Pain Severity scale; BDI, Beck Depression Inventory; ISQ, Insomnia Symptom Questionnaire; MPQ, McGill Pain Questionnaire; VAS, visual analogue scale; SF-36-M, 36-item Short Form Health Survey (Mental component); ISI, insomnia severity index; MFI, Multidimensional Fatigue Inventory; HADS-D, Hospital Anxiety and Depression Scale - Depression; HADS - A, Hospital Anxiety and Depression Scale – Anxiety; SE, sleep efficiency; FSI, Fatigue Symptom Inventory; FACT-P, Functional Assessment of Cancer Therapy Scale – Physical; FACT-E, Functional Assessment of Cancer Therapy Scale – Emotional; PFS, Piper Fatigue Scale; BPI, Brief Pain Inventory; GFS, General Fatigue Scale; POMS-D, Profile of Mood States - Depression subscale; POMS-D, Profile of Mood States - Anxiety subscale; SF-12-P, 12-item Short Form Health Survey (Physical component); SF-12-M, 12-item Short Form Health Survey (Mental component); MFSI–SF, Multidimensional Fatigue Symptom Inventory – Short Form; SCL-90-R-D, Symptom Checklist-90-Revised Depression subscale; SCL-90-R-A, Symptom Checklist-90-Revised Anxiety subscale.

Cancer patients in most of these studies were in remission having completed active treatments (chemotherapy, radiation treatment, or surgery) at least one month prior to enrolling in the study, except in two studies where patients were enrolled as they began a new regimen of chemotherapy.[50,51]

All but two studies[50,51] screened their participants' presenting sleep problems with reference to diagnostic criteria for insomnia disorder. The DSM diagnostic criteria (3rd edition, 4th edition, 4th edition text-revision[54–56]) were most commonly used as the core inclusion criteria, but there were variations between studies in terms of their specific frequency (e.g., ≥ 3 nights per week), severity (e.g., daytime impairment; Pittsburgh Sleep Quality Index Global Score > 5), and duration (e.g., ≥ 1 month, ≥ 3 months, or ≥ 6 months) cutoffs. The two studies that did not screen patients with reference to diagnostic criteria considered fatigue and poor sleep as known consequences in all phases of chemotherapy. In both of these studies, the mean Pittsburgh Sleep Quality Index Global Score at baseline were > 5 in both studies, indicating the presence of significant sleep difficulties in these patients.[57]

As part of the assessment of clinical insomnia in accordance to the DSM diagnostic criteria,[26–29,42,45,49,52,53] patients with a sleep disorder (e.g., sleep apnea) or a psychiatric Axis I disorder (e.g., psychosis, severe major depression, substance abuse disorder) that could better explain the insomnia were excluded. Some studies also specifically excluded patients who were receiving psychological treatment for insomnia, stress, anxiety, depression, or coping with pain and/or cancer outside of the RCT.[26,29,42,45,49,51,53] Subsequently, samples of patients in the current meta-analysis presented moderate levels of anxiety and depression across studies, with most samples displaying sub-threshold symptoms,[26,28,42,49–51] and a couple of samples exhibiting symptoms reaching or just crossing the suggested clinical thresholds adopted by validated questionnaires.[29,52,53]

The sleep treatments tested varied in their content, dose, duration, and delivery method. In terms of content, most treatment packages incorporated at least 1 component of CBT-I.[33,41] Psychoeducation, sleep hygiene, stimulus control, sleep restriction, cognitive therapy, and relaxation were the most frequently used components. The treatments also differed in their dose and duration, with some offering just 3 telephone intervention sessions totalling an average of 69 minutes over 60 days[51] and some offering 7 weekly sessions of 120-minute intervention.[26] Regarding delivery method, most sleep treatments tested adopted a face-to-face approach, except 2 that delivered the intervention using the phone[51] or internet.[53] Of the 9 studies that involved face-to-face contact with health care professionals, 3 delivered the treatment individually,[27,28,50] while 6 offered the treatment in groups.[26,29,42,45,49,52] The control interventions generally consisted of passive control procedures (e.g., waitlist control, treatment as usual), although 4 studies used an active control procedure (e.g., sleep hygiene advice, healthy eating control, nutrition control) and 1 was, in fact, an RCT testing whether mindfulness-based stress reduction was non-inferior to CBT-I.[45]

All studies had data on sleep and at least 2 other health and well-being outcome measures at baseline and posttreatment. Six of the RCTs also reported follow-up data at 3–12 months (maximum follow-up period: 3 months: n = 3; 6 months: n = 2; 12 months: n = 1).

Risk of Bias in Included Studies

Using the scale of Yates et al.,[46] the mean of quality score of the included RCTs was 26.00 (SD 2.58; range: 21.5–30.5), with a mean treatment quality subscore of 7.05 (SD 1.51; range: 3.5–9.0) and a mean method quality subscore of 18.91 (SD 2.36; range: 15.0–23.5) (Table 1).

Our qualitative assessment (Figure S1, supplemental material) identified a high risk of attrition bias in only 2 studies, both of which performed linear mixed model (LMM) analysis under the missing-at-random assumption to reduce biases. However, this approach was compromised when there was a pattern of missing data (due to attrition or differential attrition across groups) that could have been explained by confounding factors not controlled for, e.g., poorer health and patient's treatment preference.[45,51]

Effects of Interventions

Statistics of all analyses in this section are summarized in Table 2, with forest plots of the key analyses presented in Figure 2 and a panel of funnel plots in Figures S2–S8, supplemental material. To supplement the narrative, statistics of post hoc analyses are provided in the text.

Sleep Quality

All 11 RCTs measured improvement in sleep at posttreatment and contributed data to the pooled analysis involving 965 patients (Figure 2A). The most prevalent patient-reported outcome measure of sleep quality was the Pittsburgh Sleep Quality Index.[57] Sleep treatment was associated with a significant improvement in sleep quality at posttreatment. There was no evidence of publication bias. However, there was significant heterogeneity across the studies. A sensitivity analysis identified 2 studies, Barsevick et al.[51] and Garland et al.[45] as potential sources of the heterogeneity. By omitting these studies from the analysis, I^2 reduced from 84% to 31% and the overall effect of sleep treatment on sleep quality decreased from 0.78 to 0.68. An effect size of 0.68 suggested that an average responder to nonpharmacological treatments of insomnia would report better sleep quality than approximately 76% in the control group. This interpretation of the effect size assumed normality in the data distribution and described the overlap between the sleep treatment and control group in terms of a comparison of percentiles.

The first subgroup analysis indicated that the effectiveness of sleep treatment was significant for both cancer[42,45,50–53] and non-cancer pain patients.[26–29,49] The second subgroup analysis indicated that the effectiveness of sleep treatment was significant for studies delivering the treatment face-to-face,[26–29,42,45,49,50,52] but not for those that offered the treatment using the phone or internet.[51,53]

Six studies provided data on sleep quality at follow-up from 406 patients (range of follow-up: 3–12 months).[26,27,42,45,49,52] We found a significant overall effect of sleep treatment, which was comparable to the effect achieved by the same 6 studies at posttreatment [SMD = 0.96 (95% CI: 0.53, 1.40); Z = 4.34, P < 0.001]. Heterogeneity between studies was nonsignificant,

Table 2—Summary of findings from the main analysis, sensitivity analysis and subgroup analysis by patient type and treatment delivery method.

		Main Analysis					Sensitivity Analysis			Subgroup Analysis 1 (Patient Type)		Subgroup Analysis 2 (Delivery Method)	
Changes in		No. of Study	Tx (n)	Control (n)	Overall Effect SMD (95%CI)+	I^2 (%)	Study Removed	Subsequent Overall Effect	Subsequent I^2 (%)	Cancer Pain	Non-Cancer Pain	Internet/ Phone	Face to Face
Sleep	B-PT	11	510	455	0.78 (0.42, 1.13)***	84**	Barsevick et al. & Garland et al.	0.68 (0.46, 0.90)***	31	0.90 (0.34, 1.45)** (H)	0.67 (0.38, 0.95)***	0.89 (−0.75, 2.54)	0.79 (0.44, 1.14)***
	B-FU	6	216	190	0.98 (0.66, 1.30)***	53				1.02 (0.55, 1.49)*** (H)	0.92 (0.40, 1.45)***	n/a	0.98 (0.66, 1.30)***
Pain	B-PT	6	257	222	0.18 (0, 0.36)*	0				n/a	0.26 (−0.02, 0.54)‡	n/a	0.26 (−0.02, 0.54)‡
	B-FU	3	74	57	0.18 (−0.33. 0.70)	50				n/a	0.18 (−0.33, 0.70)	n/a	0.18 (−0.33, 0.70)
Fatigue	B-PT	6	380	341	0.38 (0.08, 0.69)**	71*	Ritterband et al. & Barsevick et al.	0.38 (0.08, 0.68)*	50	0.41 (0.06, 0.77)* (H)	n/a	0.52 (−0.59, 1.63)	0.38 (0.08, 0.68)*
	B-FU	3	121	88	0.45 (0.11, 0.78)**	27				0.59 (0.27, 0.91)**	n/a	n/a	0.45 (0.11, 0.78)**
Depression	B-PT	10	492	418	0.18 (−0.06, 0.42)	63**	Barsevick et al.	0.24 (0.06, 0.42)**	16	0.16 (−0.17, 0.48)	0.27 (−0.03, 0.57)	0.04 (−0.84, 0.92)	0.22 (0.04, 0.41)*
	B-FU	5	190	144	0.31 (0.09, 0.53)**	0				0.42 (0.16, 0.69)**	0.08 (−0.30, 0.47)	n/a	0.31 (0.09, 0.53)**
Anxiety	B-PT	7	299	247	0.04 (−0.13, 0.21)	0				0.05 (−0.16, 0.27)	0.04 (−0.38, 0.45)	n/a	0.03 (−0.15, 0.20)
	B-FU	4	158	116	0.04 (−0.24, 0.33)	27				0.12 (−0.19, 0.43)	n/a	n/a	0.04 (−0.24, 0.33)
Physical functioning	B-PT	3	230	189	0.11 (−0.37, 0.59)	75*	Espie et al.	−0.13 (−0.65, 0.40)	52	0.11 (−0.37, 0.59)	n/a	−0.13 (0.65, 0.40)	n/a
	B-FU	1	67	39	n/a	n/a				n/a	n/a	n/a	n/a
Psychosocial functioning	B-PT	4	244	196	0.55 (−0.03, 1.13)†	81**	Edinger et al.	0.14 (−0.05, 0.34)	0	0.14 (−0.05, 0.34)	n/a	0.12 (−0.15, 0.4)	1.34 (−0.95, 3.63)
	B-FU	2	81	46	2.36 (−2.19, 6.91)	96***				n/a	n/a	n/a	n/a

+Effect of nonpharmacological sleep treatment compared with control intervention, as measured in standardised mean difference (SMD) of the change. I^2 was used to quantify heterogeneity. Analyses indicating significant heterogeneity were followed up with sensitivity analysis and/or subgroup analysis, where appropriate. (H) indicates presence of significant heterogeneity in subgroup analysis. ***P < 0.001, **P < 0.01, *P < 0.05, †P = 0.06, ‡P = 0.07. B-PT, between baseline and posttreatment; B-FU, between baseline and follow up. Tx, treatment; n/a, not applicable (due to having 1 or less study in the category).

and there was no evidence of publication bias. Since all four studies included in this analysis delivered the treatment face-to-face, subgroup analysis was only carried out for patient type. Significant sleep treatment effect was found at follow-up for RCTs using both cancer pain patients[42,45,52] and non-cancer pain patients.[26,27,49]

Pain

Six of the RCTs measured improvement in pain at post-treatment and contributed to the pooled analysis involving 479 patients.[26–29,49,51] The most prevalent measure of pain was the McGill Pain Questionnaire.[58] Sleep treatment was associated with a marginally significant improvement in pain at post-treatment (Figure 2B). The overall effect size was 0.18, which suggested that an average responder to nonpharmacological treatments of insomnia would report less pain than approximately 58% in the control group. There was no evidence of publication bias and heterogeneity across studies. All but one RCT included in this analysis were conducted with non-cancer pain patients using the face-to-face approach.[26–29,49] The effects of both subgroup analyses were nonsignificant (P = 0.07).

Three RCTs reported pain improvement in 131 patients at follow-up (range: 3–6 months).[26,27,49] There was no significant improvement in pain. Neither was there evidence of publication bias nor heterogeneity between the two studies.

Fatigue

Six of the RCTs assessed improvement in fatigue at post-treatment and contributed to the pooled analysis involving 721 patients.[42,49–53] The most prevalent measure of fatigue was the Multidimensional Fatigue Scale.[59] The overall effect of sleep treatment on fatigue was significant (Figure 2C). There was no evidence of publication bias, but significant heterogeneity was detected. A sensitivity analysis revealed that by removing the studies of Ritterband et al.[53] and Barsevick et al.,[51] I^2 dropped from 71% to 50% without attenuating the effect of sleep treatment on fatigue. The overall effect size following the sensitivity analysis was 0.38, which suggested that an average responder to nonpharmacological treatments of insomnia would report less fatigue than approximately 66% in the control group.

All but one RCT included in this analysis were conducted with cancer pain patients; a significant treatment effect on

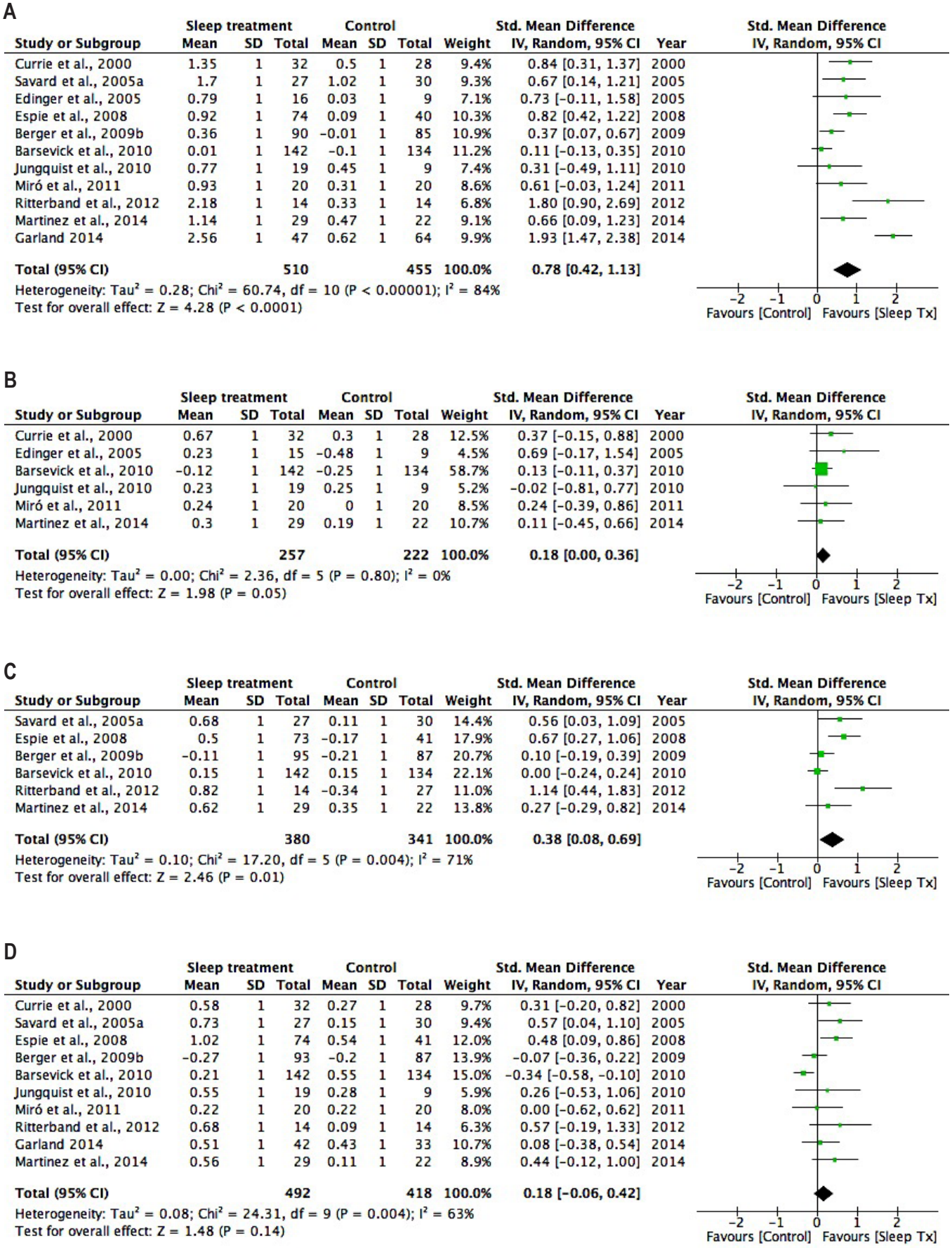

Figure 2—Forest plots summarizing the posttreatment effects of CBT on **(A)** sleep, **(B)** pain, **(C)** fatigue, and **(D)** depression.

fatigue was observed in this group of patients.[42,50–53] By delivery method, a significant effect of sleep treatment on fatigue was found for those studies delivered face-to-face[42,49,50,52] but not via the phone or internet.[51,53]

Three RCTs assessed fatigue in 209 patients at follow-up (range: 3–12 months).[42,49,52] The overall effect of sleep treatment was statistically significant and was comparable to the effect achieved by the same 3 studies at posttreatment (SMD = 0.54 [95% CI: 0.27, 0.82]; Z = 3.86, P < 0.001). There was no evidence of publication bias or heterogeneity among the three studies.

Depression

Ten of the RCTs measured depression at posttreatment and contributed to the pooled analysis involving 910 patients.[26,28,29,42,45,49–53] The most prevalent measure of depression was the Hospital Anxiety and Depression Scale.[60] No significant effect was found for the sleep treatment on depression (Figure 2D). There was no evidence of publication bias, but significant heterogeneity was detected. A sensitivity analysis revealed a drop in I^2 from 63% to 16% following the omission of the study of Barsevick et al.[51] The overall effect of sleep treatment on depression became statistically significant after the omission. The effect size was 0.24, suggesting that an average responder to nonpharmacological treatments of insomnia would report a lower level of depression than approximately 58% in the control group.

When the studies were analyzed by patient type (cancer[42,50–53] vs. non-cancer pain patients[26,28,29,45,49]), the effect of sleep treatment on depression was nonsignificant for both subgroups. When the studies were analyzed by their delivery method, the effect of sleep treatment on depression was significant for those studies that delivered the treatment face-to-face,[26,28,29,42,45,49,50,52] but nonsignificant for those that delivered the treatment using the phone or internet.[51,53]

Five RCTs measured depression in 334 patients at follow-up (range: 3–12 months).[26,42,45,49,52] A significant effect of sleep treatment was found, and the effect was comparable to that achieved by the same 5 studies at posttreatment (SMD = 0.37 [95% CI: 0.16, 0.58]; Z = 3.41, P < 0.001). There was no evidence of publication bias or heterogeneity. All studies delivered the sleep treatment face-to-face. A subgroup analysis by patient type revealed a significant effect of sleep treatment on depression in cancer pain patients,[42,45,52] but not in non-cancer pain patients.[26,49]

Anxiety, Physical Functioning, and Psychosocial Functioning

Sleep treatment effects were not significant for anxiety, physical functioning, and psychosocial functioning. Respectively, the most prevalent measure of anxiety, physical and psychosocial functioning were the Hospital Anxiety and Depression Scale[60] and the 12-item Short-Form Health Survey.[61]

DISCUSSION

Summary of Findings

The current study offers the first meta-analysis of the effect of nonpharmacological sleep interventions in conditions with chronic pain, extending two previous systematic reviews that provided narrative evaluations for the use of CBT-I for cancer[62] and non-cancer chronic pain.[63] With enhanced statistical power from the bigger aggregate sample size, our findings indicate that these sleep treatments were moderately to strongly effective in improving sleep quality in patients with cancer and non-cancer chronic pain, with a durability of up to 12-month posttreatment. A caveat is that the sleep interventions appeared to be only effective when delivered face-to-face. Future research is required to elucidate how information technology could be usefully applied to effectively deliver these interventions to the masses. A previous meta-analysis that compared the effect of telemedicine against face-to-face patient care on health outcomes found "little evidence of clinical benefits" for patient care delivered using telecommunication technologies.[64] Consistently, another recent meta-analysis evaluating the utility of computerized CBT-I for adults with primary insomnia only found a mild to moderate effect over the short term for insomnia.[65] The authors concluded that computerized CBT-I, at least for the time being, should be considered as a form of "low-intensity therapy in the stepped care model for insomnia." That said, the current meta-analysis only captured two early RCTs that used the phone or the internet to deliver sleep interventions. The small sample size might explain the nonsignificant effects in the subgroup analysis. The jury is still out on the capability of newer generations of fully automated and media-rich internet sleep treatments[66,67] and on the most cost-effective model of sleep intervention delivery.[68]

In addition to the positive effect on sleep quality, we were able to detect a mild to moderate therapeutic impact on pain immediately after nonpharmacological sleep treatments. This analgesic effect of improved sleep has not been consistently documented in individual trials, which in isolation were probably underpowered to do so. We were also able to detect a therapeutic effect of improved sleep on fatigue and depression. This observation integrates well with the broader primary insomnia literature, where we saw in a recent trial of CBT-I with older adults significant improvements in fatigue and depression at posttreatment and at 16-month follow-up.[69] The temporal association of better sleep with less pain and better mood mirrors the findings from longitudinal studies that identified untreated insomnia as a risk factor of adverse physical and mental health outcomes.[1,2,5–8,70–73] Such temporality can be interpreted as evidence for a cause role of better sleep in shaping physical and mental health. It also highlights the value of treating insomnia comorbid with chronic pain early.

The analgesic and mood-enhancing effect of improved sleep may lie with the mechanisms in the central nervous system that are shared for the regulation of arousal, pain sensitivity, mood and other related functions; candidate mechanisms proposed include the serotoninergic[74] and mesolimbic dopamine[75] systems. Improved sleep may also reduce pain and increase well-being through modulating inflammatory responses. Using the aforementioned trial of CBT-I in older adults with primary insomnia[69] as an example again, remission of insomnia was associated with a significant reduction of C-reactive protein (CRP), a clinically relevant marker of inflammation in rheumatic diseases and is prospectively linked to the development of diabetes, hypertension, and

cardiovascular disease. More experimental studies are required to confirm these hypothesized mechanisms and explore other physiological and cognitive-behavioral pathways through which improved sleep impacts on pain and mood regulation. A handful of daily process studies with chronic pain patients have revealed that nights of better sleep quality predict less attention to pain, reports of lower pain intensity in the first half of the next day, higher level of physical activity in the second half of the day, and reports of great pain in the evening.[31,73,76] Future research may wish to further investigate the role of attention and physical activity in mediating the sleep-pain relationship. Meanwhile, two treatment approaches may be pursued to capitalize on these bi-directional links. First, we could develop hybrid interventions that simultaneously address sleep and pain to optimize the treatment effects. Initial trials of such interventions have produced promising results over no treatment and the standard pain-specific treatment.[77–79] Second, it may be beneficial to deploy insomnia treatment as a preventive, health-promoting measure for a range of long-term conditions that do not have an immediate cure. More research with larger sample size and longer-term follow-up is required to determine the speed, feasibility, and cost-effectiveness of these treatment strategies.[80,81]

Limitations

Although the PRISMA guidelines were closely adhered to when conducting and reporting this meta-analysis,[47,82] the breadth and quality of the data pooled for analysis were limited by the quantity, design, and implementation of the original studies. Despite the general absence of methodological and publication biases, the above findings should be viewed with healthy scepticism as only 11 RCTs were included (we are aware of new RCTs being published since the completion of our review, e.g., Smith et al. Cognitive-behavior therapy for insomnia in knee osteoarthritis: a double blind, randomized, active placebo controlled clinical trial. Arthritis Rheumatol 2015; doi: 10.1002/art.39048), and significant heterogeneity were found in some of the analyses. Heterogeneity was considerably reduced to a nonsignificant level when one or two individual studies were removed during the sensitivity analysis. The source of heterogeneity could be traced to variations in sample populations and treatment delivery method, as illuminated by the subgroup analyses. It could also be traced to the variations in treatment duration, dosage, and content, although most included RCTs named their intervention "CBT-I." Qualitatively, we note that some trials employed treatment components that have been independently scrutinized for their clinical certainty, e.g., stimulus control, sleep restriction therapy,[33,41] while some used methods that await empirical evaluation, e.g., sleep enhancement and energy conservation advice.[51] In the current meta-analysis these interventions were evaluated as multicomponent treatment packages and random effect model was used for the estimation of treatment effect, which assumed the effect being estimated in different studies were not identical. Future research may find value in evaluating the relative merits of individual components. To this end, single-case experimental designs may be a cost-effective methodology that offers greater flexibility. Of course, within the context of RCTs, more refined subgroup analyses by treatment dosage, duration, and delivery method would also help pinpoint the sources of heterogeneity.

Sleep, pain, health, and well-being are multidimensional constructs. The current meta-analysis focused on patient-reported outcome measures (PROMS), which provided unique insights into the patients' perception of their health and the impact of the treatments they received.[83] These are subjective measures susceptible to recall and reporting biases. It would be informative if future trials would diversify the assessment methods with a broader range of subjective *and* objective outcome measures. However, with the exception of sleep for which polysomnography and actigraphy could provide established objective estimates,[84,85] it is debatable what constitutes a valid and reliable objective measurement of pain, fatigue, mood, physical, and psychosocial functioning. Related to this, we saw variations in the selection of patient-reported outcome measures across the included RCTs. We opted to use the most prevalent measure to maximize comparability. The current study did not attempt to evaluate all aspects of sleep experience because there were appreciable differences in the sleep assessment methods in terms of the technology used (sleep diary, actigraphy, or polysomnography), procedure adopted (in lab or at home; number, frequency, duration and timing of assessment) and the reporting approach (specific parameters chosen for reporting; within-group vs. between-group comparisons). We considered the possibility of aggregating data by various sleep parameters but had decided against it for concerns of high heterogeneity and practicality. Future initiatives developing consensus and recommendations for core outcome measures to be used in RCTs of nonpharmacological sleep treatments may be a way forward.[86]

CONCLUSION AND RECOMMENDATIONS

The current meta-analysis found aggregate evidence to support the use of nonpharmacological sleep interventions in cancer and non-cancer pain patients with comorbid insomnia. The evidence substantiates and extends the initial conclusion drawn in the 2006 American Academy of Sleep Medicine review on the benefit of insomnia-specific treatment in individuals with chronic pain.[41] Although the broader physical and psychological health benefits of these sleep interventions were moderate in magnitude and gradual in timing, they highlight the causal role of sleep and raise the possibility that more pro-active sleep treatment is a fruitful avenue for optimizing treatment outcomes in patients living with chronic painful conditions and for preventing the onset of adverse health outcomes. Aside from sleep researchers, these results are of particular interest to primary care physicians and allied health professionals, who are taking up an increasingly important role in preventing and managing long-term conditions. More research is now required to establish the feasibility, clinical utility, sustainability, and cost-effectiveness of such endeavors.

ACKNOWLEDGMENT

The authors thank Dr. Clemencia Rodas-Perez's for assistance in abstract translation and Dr. Helen Parsons for her statistical comments. Thanks also go to the anonymous reviewers for their helpful comments.

DISCLOSURE STATEMENT

This was not an industry supported study. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declared that the study was funded by a Research Development Fund award from the University of Warwick, UK. The funder has no role in the study design, data collection, analysis, or interpretation of data; writing of the reporting or the decision to submit the article for publication; Dr. Tang's research is funded by the National Institute for Health Research, Department of Health, UK. She has no commercial conflicts of interest to declare; Dr. Cappuccio holds the Cephalon Chair, an endowed post at Warwick Medical School, the result of a donation from the company. The appointment to the Chair was made entirely independently of the company and the postholder is free to devise his own program of research. Cephalon does not have any stake in IP associated with the postholder, and the Chair has complete academic independence from the company. He has no commercial conflicts of interest to declare; no other relationships or activities that could appear to have influenced the submitted work. The other authors have indicated no financial conflicts of interest. Authors' contributions: Dr. Tang was the principal investigator of this project, responsible for the conception and design of the study. She coordinated the data search and extraction processes, which were carried out in duplicate by Drs. Lereya and Boulton. Dr. Tang led the data analysis, drafting and final editing of the paper. Drs. Cappuccio, Wolke, and Miller were co-investigators of the project. They were involved in the design of the study and the data extraction and analysis processes. All authors contributed to the writing and final editing of the manuscript. Ethics/PRISMA statement: Ethical approval was not required for this systematic review and meta-analysis. Reporting of this manuscript closely followed the PRISMA guideline.

REFERENCES

1. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J 2011;32:1484–92.
2. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: a systematic review and meta-analysis of prospective studies. Sleep 2010;33:585–92.
3. Cappuccio FP, Miller MA. A new challenge to widely held views on the role of sleep. Ann Int Med 2012;157:593–4.
4. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry 2002;59:131–6.
5. Mork PJ, Nilsen TI. Sleep problems and risk of fibromyalgia: longitudinal data on an adult female population in Norway. Arthritis Rheum 2012;64:281–4.
6. Patel SR, Hu FB. Short sleep duration and weight gain: a systematic review. Obesity 2008;16:643–53.
7. Campbell P, Tang NK, McBeth J, et al. The role of sleep problems in the development of depression among those with chronic pain: a prospective cohort study. Sleep 2013;36:1693–8.
8. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders: an opportunity for prevention? JAMA 1989;262:1479–84.
9. Johnson EO, Roth T, Breslau N. The association of insomnia with anxiety disorders and depression: exploration of the direction of risk. J Psychiatr Res 2006;40:700–8.
10. Morphy H, Dunn KM, Lewis M, Boardman HF, Croft PR. Epidemiology of insomnia: a longitudinal study in a UK population. Sleep 2007;30:274–80.
11. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287–333.
12. Fernández A, Saameño JÁB, Pinto-Meza A, et al. Burden of chronic physical conditions and mental disorders in primary care. Br J Psychiatry 2010;196:302–9.
13. Atkinson JH, Ancoli-Israel S, Slater MA, Garfin SR, Gillin C. Subjective Sleep Disturbance in Chronic Back Pain. Clin J Pain 1988;4:225–32.
14. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Care Res 2008;59:961–7.
15. Tang NKY, Wright KJ, Salkovskis PM. Prevalence and correlates of clinical insomnia co-occurring with chronic back pain. J Sleep Res 2007;16:85–95.
16. McCracken LM, Williams JL, Tang NKY. Psychological flexibility may reduce insomnia in persons with chronic pain: a preliminary retrospective study. Pain Med 2011;12:904–12.
17. Haack M, Mullington JM. Sustained sleep restriction reduces emotional and physical well-being. Pain 2005;119:56–64.
18. Irwin MR, Olmstead R, Carrillo C, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep 2012;35:537–43.
19. Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosom Med 1976;38:35–44.
20. Smith M, Edwards R, McCann U, Haythornthwaite JA. The effects of sleep deprivation on pain inhibition and spontaneous pain in women. Sleep 2007;30:494–505.
21. Moldofsky H. Sleep and pain. Sleep Med Rev 2001;5:385–96.
22. Roehrs T, Roth T. Sleep and pain: interaction of two vital functions. Semin Neurol 2005;25:106–16.
23. Smith M, Quartana P, Okonkwo R, Nasir A. Mechanisms by which sleep disturbance contributes to osteoarthritis pain: a conceptual model. Curr Sci 2009;13:447–54.
24. 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;8:119–32.
25. Tang NKY. Cognitive-behavioral therapy for sleep abnormalities of chronic pain patients. Curr Rheum Rep 2009;11:451–60.
26. Currie SR, Wilson KG, Pontefract AJ, deLaplante L. Cognitive–behavioral treatment of insomnia secondary to chronic pain. J Consult Clin Psychol 2000;68:407–16.
27. Edinger JD, Wohlgemuth WK, Krystal AD, Rice JR. Behavioral insomnia therapy for fibromyalgia patients: a randomized clinical trial. Arch Intern Med 2005;165:2527–35.
28. Jungquist CR, O'Brien C, Matteson-Rusby S, et al. The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. Sleep Med 2010;11:302–9.
29. Miró E, Lupiáñez J, Martínez MP, et al. Cognitive-behavioral therapy for insomnia improves attentional function in fibromyalgia syndrome: a pilot, randomized controlled trial. J Health Psychol 2011;16:770–82.
30. Goforth H, Preud'homme X, Krystal A. A randomized, double-blind, placebo-controlled trial of eszopiclone for the treatment of insomnia in patients with chronic low back pain. Sleep 2014;37:1053–60.
31. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain 1996;68:363–8.
32. 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;5:355–62.
33. Morgenthaler T, Kramer M, Alessi C, et al. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. Sleep 2006;29:1415–9.
34. Okura K, Lavigne GJ, Huynh N, Manzini C, Fillipini D, Montplaisir JY. Comparison of sleep variables between chronic widespread musculoskeletal pain, insomnia, periodic leg movements syndrome and control subjects in a clinical sleep medicine practice. Sleep Med 2008;9:352–61.
35. Tang NKY, Goodchild CE, Hester J, Salkovskis PM. Pain-related insomnia versus primary insomnia: a comparison study of sleep pattern, psychological characteristics, and cognitive-behavioral processes. Clin J Pain 2012;28:428–36.

36. Eccleston C, Williams A, Morley S. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev 2009;2.
37. Montgomery P, Dennis J. Cognitive behavioural interventions for sleep problems in adults aged 60+. Cochrane Database Syst Rev 2003;1:CD003161.
38. Harvey AG, Watkins E, Mansell W, Shafran R. Cognitive behavioural processes across psychological disorders: a transdiagnostic approach to research and treatment. Oxford: Oxford University Press, 2004.
39. Smith MT, Huang MI, Manber R. Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. Clin Psychol Rev 2005;25:559–92.
40. Arcos-Carmona IM, Castro-Sanchez AM, Mataran-Penarrocha GA, Gutierrez-Rubio AB, Ramos-Gonzalez E, Moreno-Lorenzo C. [Effects of aerobic exercise program and relaxation techniques on anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia: a randomized controlled trial]. Med Clin (Barc) 2011;137:398–401.
41. Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998-2004). Sleep 2006;29:1398–414.
42. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part I: sleep and psychological effects. J Clin Oncol 2005;23:6083–96.
43. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: immunologic effects. J Clin Oncol 2005;23:6097–106.
44. Rybarczyk B, Stepanski E, Fogg L, Lopez M, Barry P, Davis A. A placebo-controlled test of CBT for co-morbid insomnia in older adults. J Consult Clin Psychol 2005;73:1164–74.
45. Garland SN, Carlson LE, Stephens AJ, Antle MC, Samuels C, Campbell TS. Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. J Clin Oncol 2014;32:449–57.
46. Yates SL, Morley S, Eccleston C, de C Williams AC. A scale for rating the quality of psychological trials for pain. Pain 2005;117:314–25.
47. Higgins J, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.
48. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160–72.
49. Martínez MP, Miró E, Sánchez AI, et al. Cognitive-behavioral therapy for insomnia and sleep hygiene in fibromyalgia: a randomized controlled trial. J Behav Med 2013:1–15.
50. Berger AM, Kuhn BR, Farr LA, et al. Behavioral therapy intervention trial to improve sleep quality and cancer-related fatigue. PsychoOncology 2009;18:634–46.
51. Barsevick A, Beck SL, Dudley WN, et al. Efficacy of an intervention for fatigue and sleep disturbance during cancer chemotherapy. J Pain Symptom Manag 2010;40:200–16.
52. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. J Clin Oncol 2008;26:4651–8.
53. Ritterband LM, Bailey ET, Thorndike FP, Lord HR, Farrell-Carnahan L, Baum LD. Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. PsychoOncology 2012;21:695–705.
54. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. Washington, DC: American Psychiatric Association, 1980.
55. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
56. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC: American Psychiatric Association, 2000.
57. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28:193–213.
58. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–99.
59. Smets E, Garssen B, Bonke Bd, De Haes J. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315–25.
60. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
61. Ware Jr JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220–33.
62. Garland S, Johnson J, Savard J, et al. Sleeping well with cancer: a systematic review of cognitive behavioral therapy for insomnia in cancer patients. Neuropsychiatr Dis Treat 2014;10:1113–24.
63. 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 2013:2049463713489384.
64. Currell R, Urquhart C, Wainwright P, Lewis R. Telemedicine versus face to face patient care: effects on professional practice and health care outcomes. Cochrane Database Syst Rev 2000;(2):CD002098.
65. Cheng SK, Dizon J. Computerised cognitive behavioural therapy for insomnia: a systematic review and meta-analysis. Psychother Psychosom 2012;81:206–16.
66. Ritterband L, Thorndike F. The further rise of internet interventions. Sleep 2012;35:737–8.
67. Espie C, Kyle S, Williams C, et al. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. Sleep 2012;35:769–81.
68. Siversten B, Vedaa Ø, Nordgreen T. The future of insomnia treatment—the challenge of implementation. Sleep 2013;36:303–4.
69. Irwin MR, Olmstead R, Carrillo C, et al. Cognitive behavioral therapy vs. Tai Chi for late life insomnia and inflammatory risk: a randomized controlled comparative efficacy trial. Sleep 2014;37:1543–52.
70. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, van den Berg JF, Verschuren WM. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. Sleep 2011;34:1487–92.
71. Lou P, Chen P, Zhang L, et al. Relation of sleep quality and sleep duration to type 2 diabetes: a population-based cross-sectional survey. BMJ Open 2012;2:2:e000956.
72. Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. Sleep 2007;30:873–80.
73. Tang NKY, Goodchild CE, Sanborn AN, Howard J, Salkovskis PM. Deciphering the temporal link between pain and sleep in a heterogeneous chronic pain patient sample: a multilevel daily process study. Sleep 2012;35:675–87.
74. Carver CS, Johnson SL, Joormann J. Serotonergic function, two-mode models of self-regulation, and vulnerability to depression: what depression has in common with impulsive aggression. Psychol Bull 2008;134:912–43.
75. Finan PH, Smith MT. The comorbidity of insomnia, chronic pain, and depression: dopamine as a putative mechanism. Sleep Med Rev 2013;17:173–83.
76. Tang NKY, Sanborn AN. Better quality sleep promotes daytime physical activity in patients with chronic pain? a multilevel analysis of the within-person relationship. PLoS One 2014;9:e92158.
77. Pigeon WR, Moynihan J, Matteson-Rusby S, et al. Comparative effectiveness of CBT interventions for co-morbid chronic pain and insomnia: a pilot study. Behav Res Ther 2012;50:685–9.
78. Tang NKY, Goodchild CE, Salkovskis PM. Hybrid cognitive-behaviour therapy for individuals with insomnia and chronic pain: a pilot randomised controlled trial. Behav Res Ther 2012;50:814–21.
79. Vitiello MV, McCurry SM, Shortreed SM, et al. Cognitive-behavioral treatment for comorbid insomnia and osteoarthritis pain in primary care: the Lifestyles Randomized Controlled Trial. J Am Geriatr Soc 2013;61:947–56.
80. Martínez-García MÁ, Soler-Cataluña JJ, Ejarque-Martínez L, et al. Continuous positive airway pressure treatment reduces mortality in patients with ischemic stroke and obstructive sleep apnea: a 5-year follow-up study. Am J Respir Crit Care Med 2009;180:36–41.

81. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatmenta cohort study. Ann Intern Med 2012;156:115–22.
82. 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.
83. Black N. Patient reported outcome measures could help transform healthcare. BMJ (Clin Res Ed) 2013;346:f167.
84. Morgenthaler T, Alessi C, Friedman L, et al. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. Sleep 2007;30:519–29.
85. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 2005;28:499–521.
86. Turk DC, Dworkin RH, Revicki D, et al. Identifying important outcome domains for chronic pain clinical trials: an IMMPACT survey of people with pain. Pain 2008;137:276–85.