Received: 10 January 2023 | Accepted: 19 January 2023

DOI: 10.1111/jsr.13847

REVIEW ARTICLE

The effect of cognitive behavioural therapy for insomnia in people with comorbid insomnia and sleep apnoea: A systematic review and meta-analysis

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Summary

Comorbid insomnia and sleep apnoea (COMISA) is a highly prevalent and debilitating sleep disorder. Cognitive behavioural therapy for insomnia (CBTi) may be an appropriate treatment for COMISA; however, no previous study has systematically reviewed and meta-analysed literature reporting on the effect of CBTi in people with COMISA. A systematic literature search was conducted across PsychINFO and PubMed ($n = 295$). In all, 27 full-text records were independently reviewed by at least two authors. Forward- and backward-chain referencing, and hand-searches were used to identify additional studies. Authors of potentially eligible studies were contacted to provide COMISA subgroup data. In total, 21 studies, including 14 independent samples of 1040 participants with COMISA were included. Downs and Black quality assessments were performed. A meta-analysis including nine primary studies measuring the Insomnia Severity Index indicated that CBTi is associated with a large improvement in insomnia severity (Hedges' $g = -0.89$, 95% confidence interval [CI] −1.35, −0.43). Subgroup meta-analyses indicated that CBTi is effective in samples with untreated obstructive sleep apnoea (OSA) (five studies, Hedges' $g = -1.19$, 95% CI −1.77, −0.61) and treated OSA (four studies, Hedges' $g = -0.55$, 95% CI −0.75, −0.35). Publication bias was evaluated by examining the Funnel plot (Egger's regression $p = 0.78$). Implementation programmes are required to embed COMISA management pathways in sleep clinics worldwide that currently specialise in the management of OSA alone. Future research should investigate and refine CBTi interventions in people with COMISA, including identifying the most effective CBTi components, adaptations, and developing personalised management approaches for this highly prevalent and debilitating condition.

KEYWORDS

Comorbid insomnia and sleep apnoea (COMISA), difficulties initiating and maintaining sleep, non-pharmacological, sleep-disordered breathing, systematic review

1 | INTRODUCTION

Insomnia and obstructive sleep apnoea (OSA) are the two most prevalent sleep disorders and frequently co-occur (Sweetman et al., 2017a). Insomnia disorder is characterised by frequent self-reported difficulties initiating and/or maintaining sleep and associated daytime impairment (The American Academy of Sleep Medicine, 2014). OSA is characterised by frequent narrowing and collapse of the upper airway during sleep (The American Academy of Sleep Medicine, 2014). These respiratory events result in reduced oxygen saturation, cortical arousals and awakenings from sleep, perceptions of non-restorative sleep, and daytime impairment. Both insomnia and OSA are associated with increased risk of mental and physical health conditions (Baglioni et al., 2011; Lechat et al., 2022a, 2022b; Li et al., 2020; Peppard et al., 2006), and incur substantial economic costs due to reduced work productivity and quality of life, and increased use of healthcare resources (Deloitte Access Economics, 2017; Natsky et al., 2020).

Insomnia and OSA have historically been viewed as independent conditions, with distinct diagnostic and management pathways. However, 30%–40% of people with insomnia have comorbid OSA, and 30%–50% of people with OSA have comorbid insomnia (Sweetman et al., 2021b; Zhang et al., 2019). In 2017, we coined the term 'comorbid insomnia and sleep apnoea (COMISA)' to define this prevalent and debilitating condition that required nuanced diagnostic and treatment considerations (Sweetman et al., 2017a). People with COMISA generally have worse sleep (Bianchi et al., 2015), daytime function (Krakow et al., 2001; Sweetman et al., 2017b; Turner et al., 2022), mental health (Lang et al., 2017), cardiovascular health (Lechat et al., 2022a, 2022b), productivity (Sivertsen et al., 2013), and quality of life (Björnsdóttir et al., 2014) compared to people with either insomnia alone, OSA alone, or neither condition. Three recent studies in large population-based cohorts have reported that people with COMISA have a 50%–70% increased risk of all-cause mortality over 10–20 years of follow-up, compared to people with neither condition (Lechat et al., 2021, 2022b; Sweetman et al., 2022a). Given the high prevalence and morbidity associated with COMISA, it is vital to develop and implement more effective treatment approaches for this condition.

Comorbid insomnia and sleep apnoea is more complex to treat compared to either condition alone (Sweetman et al., 2021a). The recommended 'first-line' treatment for OSA is continuous positive airway pressure (PAP) therapy. Patients treated with PAP wear pressurised nasal or oro-nasal masks that deliver positive air pressure during sleep to prevent airway narrowing and collapse. However, suboptimal patient acceptance and long-term adherence to PAP therapy is a significant barrier to therapy (Weaver & Grunstein, 2008). Compared to patients with OSA alone, patients with COMISA are less likely to initially accept a trial of PAP therapy, and among those that do accept PAP, people with COMISA use PAP for fewer hours per night over time (Sweetman et al., 2021a). There are several potential mechanisms, including patients with comorbid insomnia perceiving PAP as a 'threat' to their sleep (Ong et al., 2017), PAP therapy equipment causing awakenings and exacerbating pre-existing insomnia symptoms (e.g., due to noise, mask pressure, air-leaks, etc.), or patients becoming more aware of the side-effects of PAP during prolonged awakenings while wearing pressurised masks. Furthermore, many patients with COMISA experience persistent nocturnal insomnia symptoms despite PAP therapy use (Sweetman et al., 2021b), which may lead to negative perceptions of the overall benefit of PAP therapy on sleeping problems, and result in lower adherence and eventual PAP rejection. For this reason, PAP therapy as the 'first-line' treatment for COMISA often results in high rates of treatment rejection and discontinuation, and the patient disengaging with treatment. To overcome this barrier to PAP acceptance and use in patients with COMISA, it may be appropriate to initially treat the comorbid insomnia before commencing PAP therapy.

The recommended 'first-line' treatment for insomnia is cognitive behavioural therapy for insomnia (CBTi) (ASA, 2021; Qaseem et al., 2016; Riemann et al., 2017; Schutte-Rodin et al., 2008). CBTi is a multi-component therapy that aims to identify and gradually treat the underlying behavioural, cognitive, and physiological factors that maintain insomnia. It is commonly delivered over four to eight individualised treatment sessions with a therapist/psychologist, but has been adapted to group delivery (Bastien et al., 2004), tele-health delivery (Arnedt et al., 2021), self-guided reading programmes (Bjorvatn et al., 2011), interactive online programmes (Soh et al., 2020), and brief behavioural programmes (Buysse et al., 2011). CBTi improves symptoms of insomnia, daytime function, and mental health (Gebara et al., 2018), with improvements sustained long after treatment cessation (Blom et al., 2017; van der Zweerde et al., 2019).

It is possible that CBTi is less effective in patients with comorbid OSA. First, patients with COMISA may not respond to CBTi if their insomnia symptoms are a direct result of the untreated OSA. For example, respiratory events and subsequent arousals/awakenings may cause difficulties maintaining sleep. Targeted insomnia therapies such as CBTi would be expected to have less effect on improving insomnia symptoms if respiratory events continue to produce frequent awakenings, fragmented sleep architecture, and daytime impairments. Second, CBTi may be acutely effective in patients with COMISA, but have a blunted long-term impact. For example, CBTi may consolidate sleep and improve insomnia severity immediately after treatment in patients with COMISA, but untreated OSA may cause insomnia symptoms to re-emerge soon after the completion of CBTi. Third, some CBTi components may not be appropriate in people with untreated 'symptomatic' OSA (i.e., with excessive daytime sleepiness). For example, sleep restriction therapy (also *bedtime restriction therapy*), a core therapeutic component of CBTi, aims to temporarily reduce time spent in bed to increase sleep pressure, consolidate sleep periods, and reduce the association between being in bed and being awake. Increased daytime sleepiness during the first 2–3 weeks of sleep restriction therapy is a common and manageable side-effect in patients with insomnia alone and can be seen as a sign of therapeutic benefit (Kyle et al., 2014). However, patients with COMISA often enter treatment with higher daytime sleepiness, may be more vulnerable to the impacts of acute sleep restriction on alertness (Vakulin

et al., 2009), experience anxiety and reluctance to engage with sleep restriction components due to anticipated increases in sleepiness, and may experience an increased risk of sleepiness-related adverse events during the acute sleep restriction phase (Sweetman et al., 2020d). Therefore, some patients with COMISA may not be appropriate candidates for standard sleep restriction techniques that have been developed and refined in samples with insomnia alone who are less likely to present with excessive daytime sleepiness. In addition to these safety concerns, high levels of daytime sleepiness during restriction therapy may cause greater difficulties staying awake until the prescribed 'bedtime', resulting in reduced adherence to the sleep restriction protocols in patients with COMISA.

COMISA is highly prevalent in clinical and population-based cohorts, results in significant morbidity, and is more complex to manage compared to insomnia alone or OSA alone (Sweetman et al., 2017a). Comorbid insomnia symptoms reduce acceptance and use of PAP therapy (Sweetman et al., 2021a). Therefore, several research groups have suggested that patients with COMISA receive CBTi to improve insomnia and potentially increase rates of PAP acceptance and use. Several case studies and clinical trials have reported on the effectiveness of CBTi in patients with COMISA; however, no study has systematically reviewed and synthesised this literature. This is important to determine the overall effectiveness of CBTi in patients with COMISA, to identify the most appropriate CBTi modalities, settings, and treatment components, and to identify any specific sociodemographic, behavioural, or sleep parameters that are predictive of treatment response to CBTi in patients with COMISA. Therefore, the present systematic review and meta-analysis aimed to investigate and synthesise literature on the effect of CBTi on insomnia symptoms in patients with COMISA.

2 | METHODS

The protocol for this systematic review was prospectively registered on the International Prospective Register of Systematic Reviews (PROSPERO 2022 CRD42022354371). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used (Moher et al., 2009) (see PRIMSA checklist in Appendix S1: Table S1). The primary review question was 'What is the effect of CBTi on changes in insomnia symptoms in people with COMISA?'.

2.1 | Study inclusion and exclusion criteria

Study inclusion criteria were: (i) adult participants; (ii) participants with insomnia disorder/symptoms (author defined); (iii) participants with sleep apnoea (author defined); (iv) primary papers (no review papers); (v) baseline and follow-up assessments of insomnia symptoms; (vi) interventions including either; multi-component CBTi, stimulus control therapy, sleep restriction therapy, relaxation therapy, cognitive therapy for insomnia; (vii) any CBTi delivery format was acceptable (face-to-face, tele-health, self-guided online or text-based, group CBTi, eBook CBTi, blended CBTi delivery, etc.); (viii) English or German language; and (ix) peer-reviewed papers. All study designs were included to capture the full range of available literature in this area (e.g., randomised controlled trials [RCTs], chart-reviews, single-arm trials, case studies).

Additional exclusion criteria were: (i) interventions including only sleep education, motivational interviewing for PAP adherence, other cognitive/behavioural interventions for PAP adherence (not insomnia); (ii) unpublished manuscripts, presentations, grey literature, or conference abstracts; and (iii) review papers, protocol papers, preprints, protocol registrations.

2.2 | Literature search strategy

Hand-searching and piloting of search terms was completed prior to authors finalising search terms, databases, and search strategy. A systematic search of terms relating to 'Insomnia' AND 'Sleep apnoea' AND 'CBTi' (and alternative terms, spelling, derivatives of each component; see supplement) was conducted in PubMed and PsychINFO. Range in publication dates for PubMed was 1982 to November 2022, and for PsychINFO was 1989 to November 2022.

2.3 | Screening

All articles were screened at title/abstract and full-text stage according to the above inclusion and exclusion criteria by at least two authors, and any conflicts were resolved by a third author. Cohen's κ and the percentage agreement between authors were calculated at each stage.

2.4 | Data extraction and quality assessment

All data were extracted and verified by at least two authors. Extracted data included; first author, year of publication, study design, insomnia assessment criteria and baseline severity, OSA assessment criteria and baseline severity, COMISA sample characteristics (age, body mass index [BMI], gender, race), details about the CBTi intervention, comparator sample and/or group details (if relevant; e.g., insomnia-only control, or no-treatment control), primary outcome measure, pre- and post-treatment insomnia severity for intervention (and control group/s where relevant).

For studies with sequential interventions of CBTi prior to PAP therapy, only data from the follow-up assessment before commencing PAP are reported. Details are provided to identify studies of concurrent CBTi and sleep apnoea interventions where it was not possible to isolate the unique effect of CBTi intervention on change in insomnia symptoms.

The Downs and Black checklist (Downs et al., 1998) was used to assess study quality (suitable for quality assessment of non-RCTs). Sub-scores were calculated for each study for; Reporting (10 items),

External validity (three items), Internal validity – Bias (seven items), Internal validity – Confounding (six items), and Power (one item). An additional item was added on whether funding source/s were reported (Yes = 1 point, No = 0 points). A score of '0' was allocated for any items that were not relevant to a given study, for consistency of reporting. Sub-scores and total scores (ranging from 0 [lowest score] to 33 [highest score]) were calculated for each study.

2.5 | Statistical analysis (meta-analysis)

Data were extracted on insomnia severity before and after CBTi in order to synthesise treatment effects using Meta-Essentials tools (https://www.erim.eur.nl/research-support/meta-essentials/) (Suurmond et al., 2017), the mean and standard deviation (SD) of the Insomnia Severity Index (ISI) before and after treatment were extracted; where mean and SD data were not available, Cohen's *d* was used. To determine the heterogeneity of the studies the I^2 statistic was reported, with a value of 25 indicating low, 50 medium and 75 indicating high heterogeneity (Huedo-Medina et al., 2006). Considering the small sample size of included studies, the 95% confidence intervals (CIs) around I^2 were reported. Anticipating large heterogeneity a random effects model was used. The magnitude of the effect was judged by computing Hedges' *g*. Publication bias was evaluated by examining the Funnel plot and Egger's regression.

3 | RESULTS

3.1 | Study selection

Figure 1 indicates the PRISMA flow diagram of the search strategy and screening process. The literature search indicated 348 records. Removal of 53 duplicates resulted in 295 unique records for title and abstract screening. Cohen's κ ranged from 0.78 to 1.00 and the percentage agreement was between 97% and 100%; both statistics indicate high inter-rater agreement (McHugh, 2012). Main exclusion reasons were: not a primary research paper ($n = 173$), not an intervention study ($n = 40$), no CBTi component in the intervention ($n = 24$), and not an adult sample ($n = 16$). In all, 27 records were retained for full-text review. At full-text stage, one study was excluded because the intervention did not contain a CBTi component, one did not have follow-up data on insomnia, three did not include a COMISA sample, and three did not include insomnia symptoms as an outcome measure. The percentage agreement at this stage varied between 50% and 100% (low values were due to small number of studies that were excluded at this stage). A total of 19 records were eligible for data

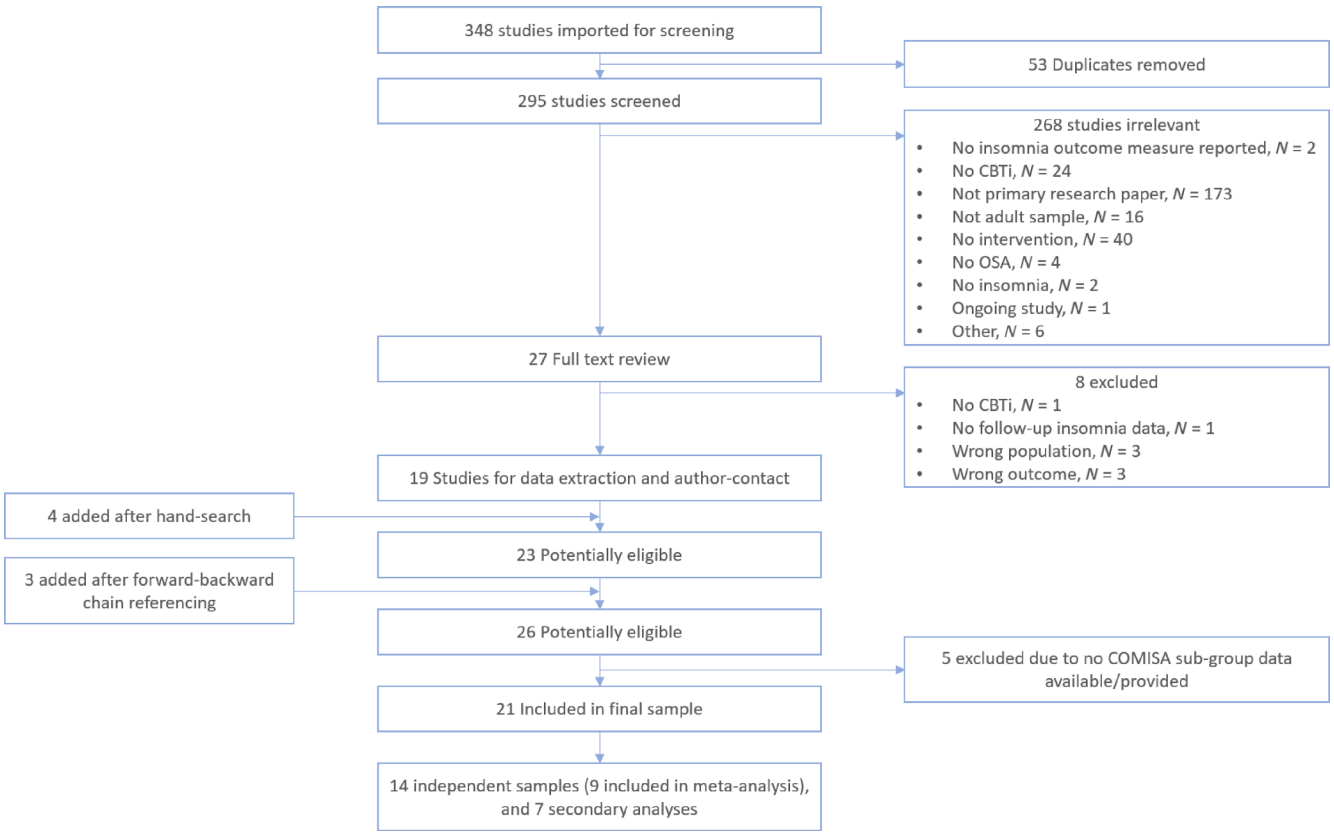

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. CBTi, cognitive behavioural therapy for insomnia; COMISA, comorbid insomnia and sleep apnoea; OSA, obstructive sleep apnoea. [Color figure can be viewed at wileyonlinelibrary.com]

extraction. Four additional records were identified via hand-search and deemed eligible, resulting in 23 eligible records. Forward- and backward-chain searching of potentially eligible records resulted in additional inclusion of four articles that were deemed eligible. Authors of six identified studies were contacted to provide COMISA subgroup insomnia severity data at pre- and post-treatment. Five records were removed due to COMISA subgroup data being unavailable or not provided after requesting them. Thus, 21 independent records were included in the final sample.

3.2 | Samples

The COMISA sample sizes had a wide range across studies from one to 141, owing to the inclusion of case reports. The samples were adults only, with a mean age ranging from 31 to 72 years across all trials. Military personal and veterans were represented in three studies (Alessi et al., 2021; Fung et al., 2016; Hoyt et al., 2022), whilst 10 studies included community/sleep clinic samples (An & Chung, 2010; Bjorvatn et al., 2018; Guilleminault et al., 2008; Iwashita et al., 2022; Ong et al., 2020, 2017; Redeker et al., 2022; Sweetman et al., 2017b; Sweetman et al., 2019b; Wickwire et al., 2008), and another specifically recruited trauma survivors (Krakow et al., 2004). The remaining seven studies were secondary analyses from primary papers (Bensen-Boakes et al., 2022; Tu et al., 2022; Sweetman et al., 2020a, 2020b, 2020c, 2020d, 2021c).

3.3 | Sociodemographic characteristics (age, sex, race, BMI)

The military samples (Alessi et al., 2021; Fung et al., 2016; Hoyt et al., 2022) were overwhelming male, ranging from 89% to 97% male across all trials. Excluding the case studies, community/sleep clinic samples were somewhat more balanced, ranging from 37%–71% male. Overall, most studies included more male than female participants. The studies were a mix of races, as five studies contained ≥75% White participants. A further three were <50% White and one case study was with an individual of Asian ethnicity. BMI was reported in seven studies, with mean values ranging from 23 to 36 kg/m^2.

3.4 | Study design and study quality

Six studies used non-randomised trial designs, including two case reports (An & Chung, 2010; Wickwire et al., 2008), and four retrospective chart reviews (Hoyt et al., 2022; Iwashita et al., 2022; Krakow et al., 2004; Sweetman et al., 2017b). There were seven RCTs. Two trials randomised individuals to CBTi alone or a comparator including sleep education control (Fung et al., 2016) and a surgical intervention for OSA (Guilleminault et al., 2008). In three RCTs CBTi was combined with PAP therapy and compared to either PAP alone (Ong et al., 2020; Sweetman et al., 2019b), or PAP therapy with sleep hygiene advice (Bjorvatn et al., 2018). In one RCT, CBTi was combined with a PAP adherence programme and compared to PAP with a sleep education programme (Alessi et al., 2021). In one study, individuals were randomised to CBTi versus self-management education group (Redeker et al., 2022), for this study, subgroup data for patients with OSA who were on PAP were extracted. Quality assessment results of primary articles are reported in Appendix S1: Table S2. Total quality scores ranged from 10 to 29.5 (out of a possible score of 33), with a mean (SD) score of 23.0 (6.8).

3.5 | Diagnosis of COMISA

3.5.1 | Insomnia

In all, 11 studied diagnosed insomnia according to clinical interview (Alessi et al., 2021; An & Chung, 2010; Fung et al., 2016; Guilleminault et al., 2008; Iwashita et al., 2022; Krakow et al., 2004; Ong et al., 2020, 2017; Sweetman et al., 2017b, 2019b; Wickwire et al., 2008). One study used medical records (Hoyt et al., 2022). Two studies used validated questionnaire cut-offs (Bjorvatn et al., 2018; Redeker et al., 2022). Baseline insomnia severity varied between studies based on sample population and inclusion criteria (see Tables 1 and 2 for detailed descriptions of insomnia severity).

3.5.2 | Obstructive sleep apnoea

To diagnose OSA, in-laboratory full polysomnography (PSG) was conducted in five studies (An & Chung, 2010; Guilleminault, 2008; Krakow et al., 2004; Ong et al., 2020, 2017), three studies used the diagnosis of OSA in medical records/sleep study reports (Hoyt et al., 2022; Iwashita et al., 2022; Wickwire et al., 2008), and two studies diagnosed OSA through a home sleep study (Bjorvatn et al., 2018) or WatchPAT home study (Fung et al., 2016). Three studies used a combination of in-laboratory and/or home-based PSG (Alessi et al., 2021; Sweetman et al., 2017b, 2019b) and one study used a mix of medical report review, Level 3 ambulatory screening and existing PAP treatment (Redeker et al., 2022). The apnoea–hypopnea index (AHI) cut-off used for OSA diagnosis (e.g., AHI ≥5, or AHI ≥15 events/h) varied by study resulting in different levels of baseline OSA severity (see Tables 1 and 2 for details).

3.6 | Type of insomnia metrics used

In all, 11 trials included the ISI as one of the primary outcome measures (Alessi et al., 2021; Bjorvatn et al., 2018; Hoyt et al., 2022; Iwashita et al., 2022; Krakow et al., 2004; Ong et al., 2020, Ong et al., 2017; Redeker et al., 2022; Sweetman et al., 2017b, 2019b; Wickwire et al., 2008). This was often used in conjunction with other measures including other validated insomnia scales, sleep diaries

TABLE 1 Primary non-randomised trials investigating the effect of cognitive behavioural therapy for insomnia in patients with comorbid insomnia and sleep apnoea

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated/untreated	COMISA sample: sample, *n*; age, years, mean (SD); gender, %; race; BMI, kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/ severity. Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Krakow et al. (2004)	Retrospective chart review	Diagnosis of psychophysiological insomnia	In-laboratory PSG diagnosis of SDB Minimum AHI eligibility threshold not specified	Trauma survivors $N = 17$, age = 42.88 (13.10), 76% female, BMI = 26.1 (12.82)	N/A	CBTi programme	ISI; PSQI; FOSQ	Pre- and post-treatment ISI data not reported. Effect size was $d = 1.53$, and 8 of 17 participants (47%) reported ISI scores ≤10 by post-treatment	N/A
Wickwire et al. (2008)	Case report	Clinical interview, ISI = 22	Sleep study report, moderate-to-severe OSA	$N = 1$; 'slightly overweight' white male in his 60s	N/A	Psychologist-delivered CBTi plus motivational enhancement for PAP adherence (nine combined sessions) CBTi components included: sleep education, stimulus control, developing a pre-sleep routine, cognitive therapy, relaxation	ISI; sleep diary time awake in bed, sleep efficiency	1 month: improvements in sleep efficiency, SOL and WASO, ISI and PAP use. Pre-treatment ISI = 22; post-treatment ISI = 16	N/A
An and Chung (2010)	Case report	Clinical interview	In-laboratory PSG, AHI = 74.6	Civilian; ($N = 1$), age = 63, female, BMI = 22.6, Asian	N/A	CBT (details not provided) concurrent with pharmacological management	N/A	Improved symptoms (no details provided)	N/A

TABLE 1 (Continued)

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated/untreated	COMISA sample: sample, *n*; age, years, mean (SD); gender, %; race; BMI, kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/ severity. Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Ong et al. (2017)[a]	Prospective observational trial	Psychologist diagnosis according to ICSD-2 insomnia criteria ISI = 18.59(4.95)	AHI ≥5 events/h sleep on in-laboratory PSG. AHI mean = 36.8 (36.2)	COMISA *N* = 34 (19/34 participants received CBTi), age = 59.1(11.7), 58% female, BMI = 36.0 (10.1), Race: 42% White; 47% Black; 11% Asian	N/A	Components not described, BSM expert delivered, maximum eight sessions, mean (SD) of 3.3 (2.11) sessions attended	ISI, sleep diary parameters, questionnaire measures of fatigue, anxiety, DBAS, depression, pre-sleep arousal	Outcome data from 19 patients that received CBTi with or without PAP are reported here (16 with PAP therapy are reported in the meta-analysis section) Pre-treatment ISI = 18.59 (4.95) Follow-up ISI = 15.47 (6.37)	N/A
Sweetman et al. (2017b)[a]	Retrospective chart review	Psychologist diagnosis	In-laboratory or home-based PSG COMISA was defined as an AHI ≥5 events/h sleep	COMISA (*N* = 141), age = 57.73 (14.83), gender = 59.6% female, BMI = 27.89 (4.93)	Patients with insomnia alone confirmed via overnight sleep study AHI <5 events/h sleep Insomnia alone (*N* = 314), age = 48.97 (15.27), gender = 89.4% female, BMI = 25.55 (4.77)	Psychologist-delivered CBTi programme 2-h group education session followed by 4–6 individualised treatment sessions covering cognitive, behavioural, and educational components	ISI, 1-week sleep diary parameters, ESS, Flinders Fatigue Scale, DBAS, Depression Anxiety and Stress Scale	Pre-treatment ISI = 18.0 (5.7); post-treatment ISI = 9.6 (7.1); 3-month follow-up ISI = 8.2(7.3)	Insomnia alone control Pre-treatment ISI = 19.9(6.4); post-treatment ISI = 9.5(7.8); 3-month follow-up ISI = 7.6(7.8)
Iwashita et al. (2022)	Retrospective chart review	Psychiatrist diagnosis of chronic insomnia according to ICSD-3 criteria	OSA diagnosis in medical records. All patients had commenced PAP therapy prior to starting CBTi Minimum AHI eligibility threshold not specified	5 patients that completed full CBTi programme, age = 59.8(13.5), gender = 20% female, BMI not reported	Patients with insomnia alone (no comorbid psychiatric or medical condition in medical records) No sleep study to rule-out undiagnosed OSA in comparator group	Psychologist-delivered five-session CBTi programme, 50 min/session. Sleep education, progressive muscle relaxation, sleep restriction, stimulus control therapy. No information on PAP therapy	ISI, sleep diaries, DBAS	[a] Pre-treatment ISI = 14.8 (5.9) Post-treatment ISI = 14.8 (6.8) Small changes in diary-measured TST (mean = 15.2 min), sleep efficiency (mean = 4.8%), SOL (mean = 7.8 min), and WASO (mean = 6.2 min)	Insomnia alone control. Pre-treatment ISI = 16.0(3.6) Post-treatment ISI = 8.1(3.9)

(Continues)

TABLE 1 (Continued)

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated/untreated	COMISA sample: sample, *n*; age, years, mean (SD); gender, %; race; BMI, kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/ severity. Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Hoyt et al. (2022)	Single-arm retrospective chart review	DSM-IV-TR criteria for insomnia (medical records)	Diagnosis of OSA (medical records) Minimum AHI eligibility threshold not specified 37% defined as adherent (PAP use on ≥4 h/ night on ≥70% of nights), 38.3% as suboptimal adherence, and 24.7% without PAP information	73 active military personnel with COMISA treated with CBTi at sleep disorders clinic. Age = 36.2(7.5), 89% male, BMI not reported; 41% White	N/A	Individualised CBTi, mean number of sessions attended = 4.9 Components, therapists, session duration not described	ISI; diary-measured sleep parameters	Pre-treatment ISI = 17.1 (4.4). Post-treatment ISI =15.2 (5.9) Significant improvement in SOL, WASO, sleep efficiency, number of awakenings, ISI pre- to post-treatment	N/A

Abbreviations: AHI, apnoea–hypopnoea index; BMI, body mass index; CBTi, cognitive behavioural therapy for insomnia; COMISA, comorbid insomnia and sleep apnoea; DBAS, Dysfunctional Beliefs and Attitudes About Sleep Scale; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; ICSD-3, *International Classification of Sleep Disorders*, Third Edition; ISI, Insomnia Severity Index; N/A, not available; OSA, obstructive sleep apnoea; PAP, positive airway pressure; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RDI, respiratory disturbance index; SDB, sleep disordered breathing; SOL, sleep onset latency; TST, total seep time; WASO, wake after sleep onset.

[a]Data provided by authors.

TABLE 2 Primary randomised controlled trials investigating the effect of cognitive behavioural therapy for insomnia in patients with comorbid insomnia and sleep apnoea

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment, inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated-untreated	COMISA sample: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/severity.Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Guilleminault et al. (2008)	Parallel crossover RCT of CBTi and surgical treatment of OSA. Only the first treatment-phase is reported in this Table (CBTi versus. surgery)	Clinical interview consistent with chronic insomnia disorder; sleep diaries	In-laboratory sleep study; AHI = 7.9 (4.8) Minimum AHI eligibility threshold not specified	Civilians; *N* = 30; age = 31(5); 37% male; BMI = 24(2); race not reported	Surgical intervention for OSA	Group CBTi (seven sessions over 9 weeks).	In-laboratory sleep study parameters (SOL, WASO, TST, sleep stages); sleep diaries	Shorter SOL was only noted after CBTi independent of treatment sequence; TST improved in both treatment sequences No ISI data	CBTi: pre-CBTi PSG SOL = 27(9); WASO = 40(22); TST = 373(16); post-CBTi SOL 12(2); WASO = 20 (8); TST = 390 (7) OSA surgery: pre-surgery SOL = 26(10); WASO = 45(18); TST = 374(16); post-surgery SOL = 22(10); WASO = 8(2); TST = 405(7)
Fung et al. (2016)	Mixed 2 (CBTi, vs sleep education) by 2 (mild OSA, no OSA) design	Structured clinical interview fulfilling ICSD-2 chronic insomnia disorder criteria	WatchPAT home sleep study; AHI 10.1(3.0) Mild OSA was defined as a AHI of ≥5 to <15 events/h	Military veterans; *N* = 134 (95 with mild OSA); age = 72(8); 97% male; BMI not reported; 78% White	Sleep education	Individual or group CBTi provided by health educator (five sessions in 6 weeks)	Sleep diary and actigraphy SOL, WASO, total wake time, sleep efficiency, and total PSQI	6 months: participants with mild OSA in the CBTi group had improvements in SOL and PSQI score as compared to education alone. There was no interaction between OSA status and treatment arm for CBTi treatment effects	Group with mild OSA receiving education alone. Pre-treatment: sleep diary SOL = 47 (95% CI 35–60); WASO = 63(95% CI 48–79); sleep efficiency = 70 (95% CI 66–75); PSQI = 9.4(95% CI 8.4–10.4). Post-treatment: sleep diary SOL = 21 (95% CI 17, 24); WASO = 35 (95% CI:22, 48); sleep efficiency = 84 (95% CI 81,87); PSQI = 5.7 (95% CI 4.6, 6.8)

(Continues)

TABLE 2 (Continued)

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment, inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated-untreated	COMISA sample: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/severity.Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Bjorvatn et al. (2018)	Parallel-arm RCT	Insomnia was diagnosed based on the Bergen Insomnia Scale	Home sleep study, AHI = 25 (19) events/h Inclusion criterion AHI ≥5 events/h Participants were currently initiating PAP therapy	Civilians; *N* = 164; age = 56(12); 71% male; BMI = 32(6); race not reported	Sleep hygiene information	Self-guided CBTi book (56% agreed they read the book)	Bergen Insomnia Scale, ISI	3 months: among people treated with PAP; insomnia symptoms improved similarly in those given CBTi book versus sleep hygiene. No time by condition interaction. Pre-treatment ISI =16.6(4.4) Post-treatment ISI = 13.6(5.5); effect size was *d* = 0.60	Pre-treatment ISI = 17.0(4.0); post-treatment ISI = 14.1(5.8); effect size was *d* = 0.58
Sweetman et al. (2019b)	Parallel-arm RCT	Psychologist diagnosis of insomnia according to ISI, 1-week sleep diary, daytime function questionnaires. ISI = 18.2(5.0)	In-laboratory/home-based sleep study, AHI = 34.5 (21.9) events/h Inclusion criteria: Untreated OSA, AHI ≥15 events/h and sleep physician recommendation of PAP therapy	Sleep clinic patients with COMISA (*n* = 145); age = 58.2(9.9); 44.8% female; BMI = 35.3(6.4); 96% White	No treatment control	Psychologist delivered four-session CBTi programme (individual/group or both), including sleep education, PSG feedback (sleep-state-discrepancy), sleep restriction therapy, relapse prevention	ISI, sleep diaries, daytime function questionnaires	CBTi group reported a greater reduction in global insomnia severity, and greater improvement in sleep diary parameters than control at post-treatment. CBTi group: pre-treatment ISI = 18.5(5.3) post-treatment ISI = 12.0(5.1)	No-treatment control group. Pre-treatment ISI = 17.9(5.3). Post-treatment ISI = 16.4(6.0)

TABLE 2 (Continued)

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment, inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated-untreated	COMISA sample: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/severity.Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Ong et al. (2020)	Three-arm RCT	Structured clinical interview meeting ICSD-2 insomnia disorder criteria and SOL or WASO ≥30 min ≥3x/week on sleep diary	In-laboratory sleep study followed by in-laboratory PAP titration; AHI = 24 (21) events/h Inclusion criteria: AHI ≥5 to <100 events/h sleep	Civilians; *n* = 118; age = 50(13); 47% male; BMI not reported; 49% White	PAP with sleep self-monitoring (C); also used in Phase I of condition B. Attrition: A-7.3% B-12.8% C-13.2%.	Therapist-delivered four-session individual CBTi (sleep restriction, stimulus control, sleep hygiene, cognitive therapy) prior to PAP initiation (A) or concurrently with PAP (B)	ISI, PSQI	90-days after PAP initiation: CBTi arms (A + B) had greater improvements in insomnia severity and sleep quality than PAP alone (C). PAP use was not improved by CBTi alone; Arm A: pre-treatment ISI = 17.1(4.7) post-treatment ISI = 6.5(5.8) Arm B: pre-treatment ISI = 17.4(5.0); post-treatment ISI = 5.8(4.7).	Arm C (PAP alone) Pre-treatment ISI = 17.7(5.2); post-treatment ISI = 8.7(6.4)
Alessi et al. (2021)	Parallel-arm RCT	Structured clinical interview meeting ICSD-3 chronic insomnia disorder criteria; ISI = 14 (5)	Home sleep study (87%); In-laboratory PSG (13%); AHI = 35 (21) events/h Inclusion criteria: AHI ≥15 events/h sleep	Military veterans; *n* = 125; age = 63 (7); 96% male; BMI not reported; 39% White	PAP with sleep education programme delivered by sleep coach; session attendance: Intervention 84% versus control 97% ($p = 0.014$)	Individual CBTi with a PAP adherence program (five weekly sessions) delivered by a sleep coach (supervised by BSM specialist)	ISI, PSQI, sleep diary SOL, WASO, sleep efficiency; actigraphy sleep efficiency	3 and 6 month follow-up: intervention group had greater improvement in insomnia severity, sleep quality, SOL, sleep efficiency and higher PAP use than control. Pre-treatment ISI = 13.9 (95% CI 12.6–15.2); 6-month ISI = 7.7 (95% CI 6.1–9.3)	Control group Pre-treatment ISI = 13.2(95% CI 11.9–14.5); 6-month ISI = 10.1(95% CI 8.6–11.7)

(Continues)

TABLE 2 (Continued)

Study	Study design	Insomnia: assessment, inclusion criteria, and severity at baseline, mean (SD)	OSA: assessment, inclusion criteria (AHI/RDI), severity at baseline; AHI mean (SD), treated-untreated	COMISA sample: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	Comparator sample/group: sample *n*; age, years, mean (SD); gender, %; race; BMI kg/m^2, mean (SD)	CBTi description: duration, number of sessions, provider/s, components	Primary insomnia outcome measure/s	Outcome: time until follow-up, change in insomnia symptoms/severity.Mean (SD) ISI at pre- and post-treatment (and follow-up)	Outcome for control group: mean (SD) ISI at pre- and post-treatment (and follow-up)
Redeker et al. (2022)	Mixed 2 (CBTi versus education control) by 2 (PAP-treated OSA versus no/mild OSA) factorial design	Participants with chronic heart failure (based on medical records), with an ISI score of ≥8	Apnoea Risk Evaluation System (Watermark Medical, Inc.) Information about previous sleep apnoea diagnosis and PAP use in medical record	91 participants with PAP-treated OSA Age, gender, race, BMI information of COMISA group not provided	Education control (healthy heart/healthy lifestyle information)	Four bi-weekly face-to-face CBTi sessions with a psychiatric nurse practitioner trained in CBTi Stimulus control, sleep restriction, sleep hygiene, cognitive therapy, progressive muscle relaxation, (optional) hypnotic tapering, and relapse prevention	ISI, PSQI, actigraphy sleep parameters, daytime function questionnaire	Among participants with PAP-treated OSA, those in the CBTi group reported a significantly greater ISI improvement (6.64-point reduction, ±0.69 standard error)	In the control group the reduction was 4.88 (±0.71 standard error) on the ISI from pre- to post-treatment

Abbreviations: AHI, apnoea–hypopnoea index; BMI, body mass index (kg/m^2); CBTi, cognitive behavioural therapy for insomnia; CI, confidence interval; COMISA, comorbid insomnia and sleep apnoea; BSM, Behavioural Sleep Medicine; ICSD-3, *International Classification of Sleep Disorders*, Third Edition; ISI, Insomnia Severity Index; OSA, obstructive sleep apnoea; PAP, positive airway pressure; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RCT, randomised controlled trial; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset.

metrics (sleep onset latency [SOL], wake after sleep onset [WASO], total seep time [TST], etc.), actigraphy or the Pittsburgh Sleep Quality Index (see Tables 1 and 2 for details). Collection of insomnia symptoms was not applicable in one trial, which was excluded at full-text review (Stahl et al., 2022).

3.7 | Treatment components included in CBTi

The CBTi was delivered individually (Alessi et al., 2021; Hoyt et al., 2022; Ong et al., 2020; Redeker et al., 2022), in groups (Guilleminault et al., 2008), in groups and individually (Fung et al., 2016; Sweetman et al., 2019b) or a combination of both for each patient (Sweetman et al., 2017b); others did not provide details on treatment delivery. One study included a self-help book (Bjorvatn et al., 2018). The number of sessions of CBTi (when reported) varied between four and nine (see Tables 1 and 2 for details). CBTi was delivered by a psychologist/trained therapist (Iwashita et al., 2022; Ong et al., 2020, Ong et al., 2017; Sweetman et al., 2017b, 2019b; Wickwire et al., 2008), one study provided the intervention through a sleep coach with Behavioural Sleep Medicine specialist assistance (Alessi et al., 2021), and a psychiatric nurse practitioner trained in CBTi delivered the intervention in another study (Redeker et al., 2022). Patients were also on PAP therapy either concurrently or after CBTi in some studies (Alessi et al., 2021; Bjorvatn et al., 2018; Ong et al., 2020, Ong et al. 2017; Redeker et al., 2022; Sweetman et al., 2019b; Wickwire et al., 2008). In studies that listed individual components, the core components were sleep restriction, stimulus control, relaxation, cognitive therapy, and sleep education (see Tables 1 and 2 for details).

3.8 | Side-effects of treatment

Of the RCTs, only two reported adverse events in the CBTi arms. In Sweetman et al. (2019b), 16.7% of adverse events were considered serious (and unrelated), but this was not different to the rates in the control group. No accidents or extreme daytime sleepiness were reported in the CBTi arm. In a secondary analysis of these RCT data, Sweetman et al. (2020d) investigated changes in self-reported daytime sleepiness during each session of CBTi. Participants in the CBTi group reported a small increase in sleepiness following the first week of sleep restriction therapy, which returned to baseline levels over subsequent weeks. Daytime sleepiness is more commonly considered a sign of therapeutic effect during CBTi, rather than a 'side-effect' per se. In Ong et al. (2020), 12 and 13 adverse events related to the intervention/protocol were reported in the two arms in which CBTi was administered. This was not considered different to the arm with no CBTi (n = eight). These events were not categorised as serious adverse events. In an ancillary study of this RCT, Turner et al. (2022) found poorer performance in neurocognitive functioning after completing CBT-I compared to baseline. This may have been a result of sleep deprivation typically associated with sleep restriction therapy. This study was not identified in the searches, because it is only at preprint.

3.9 | Sociodemographic predictors of treatment response

The trials investigating secondary outcomes (Table 3) indicated predictors of treatment response in four out of seven studies. Commonalities included symptoms of depression, anxiety, and stress not predicting treatment response to CBTi when compared with control groups (Sweetman et al., 2020b, 2020c). One study indicated that CBTi was associated with reduced insomnia symptoms in patients with a higher AHI, less WASO and less Stage 3 sleep on PSG (Sweetman et al., 2021c). Being younger was associated with lower WASO and better sleep efficiency, whilst being unmarried was related to higher WASO and less overall sleep (Tu et al., 2022). Mild OSA was associated with longer actigraphy sleep time but reduced self-reported sleep quality when compared with moderate OSA (Tu et al., 2022). In a secondary analysis of the Sweetman et al. (2020a) RCT data, it was reported that CBTi led to a greater AHI reduction, versus no-treatment control in patients with untreated COMISA. It was suggested that the effect of CBTi on reduced OSA severity may be mediated by consolidated sleep periods, improved transition to stable sleep, and reduced likelihood of premature arousals/awakenings to respiratory stimuli (respiratory arousal threshold). In another secondary paper, CBTi did not impact patterns of sleep–wake state discrepancy, versus no-treatment control (Bensen-Boakes et al., 2022).

3.10 | Meta-analysis of the effect of CBTi on insomnia severity in patients with COMISA

Nine studies reported sufficient data on pre- to post-treatment changes in insomnia severity to enable a meta-analysis on the effects of CBTi on insomnia symptoms in patients with COMISA (Alessi et al., 2021; Bjorvatn et al., 2018; Hoyt et al., 2022; Iwashita et al., 2022; Krakow et al., 2004; Ong et al., 2020, 2017; Sweetman et al., 2017b, 2019b). The weighted pooled effect size for these studies was large (Hege's $g = -0.89$; 95% CI −1.35, −0.43, $p < 0.001$). The Forest plot is presented in Figure 2. The heterogeneity of the studies included was large ($I^2 = 87.79\%$, 95% CI 69.40%, 90.69%). Therefore, two subgroup analyses were conducted in which the effects were investigated when CBTI was either delivered alone (Hedges' $g = -1.19$; 95% CI −1.77, −0.61) (Iwashita et al., 2022; Krakow et al., 2004; Ong et al., 2020; Sweetman et al., 2017b, 2019b) or in combination with treatment for the OSA (Hedges' $g = -0.55$; 95% CI −0.75, −0.35) (Alessi et al., 2021; Bjorvatn et al., 2018; Hoyt et al., 2022; Ong et al., 2017). The heterogeneity in the combined treatment subgroup improved slightly (I^2 for CBTi combined: 44.2%) but remained high for the isolated CBTi subgroup (I^2 for CBT isolated group: 83.33%). The Forest plots for subgroup analyses are presented in Figure 3.

TABLE 3 Trials investigating secondary outcomes and/or moderators of the effect of cognitive behavioural therapy for insomnia in patients with comorbid insomnia and sleep apnoea

Study	Primary study	Study aim	Secondary outcome	Predictors of treatment response
Sweetman et al. (2020d)	Sweetman et al. (2019b)	Investigate week-to-week changes in sleep parameters and daytime sleepiness during CBTi sessions in patients with COMISA	CBTi is associated with a small increase in self-reported daytime sleepiness during the first week following sleep restriction therapy commencement. Daytime sleepiness subsequently returns to baseline levels	N/A
Sweetman et al. (2020a)	Sweetman et al. (2019b)	Investigate the effect of CBTi, versus control, on changes in sleep apnoea severity in patients with COMISA	Compared to no-treatment control, CBTi was associated with a greater reduction in sleep apnoea severity, across sleep stages and postures	N/A
Sweetman et al. (2020c)	Sweetman et al., (2017b)	Investigate the effect of symptoms of depression, anxiety, and stress at baseline on treatment-response to CBTi in patients with insomnia alone and COMISA	N/A	Symptoms of depression, anxiety and stress at baseline were not associated with treatment-response to CBTi, between those with insomnia alone and COMISA
Sweetman et al., (2020b)	Sweetman et al. (2019b)	Investigate effect of depression, anxiety, and stress symptoms in moderating effect of CBTi versus control in patients with COMISA	N/A	Symptoms of depression, anxiety and stress at baseline did not predict treatment-response to CBTi, versus control, in 145 patients with COMISA
Sweetman et al. (2021c)	Sweetman et al. (2019b)	Identify baseline PSG features that are predictive of treatment-response to CBTi, versus control in patients with COMISA	N/A	Compared to control, CBTi was associated with greater improvement in insomnia (ISI) in patients with; higher AHI, less WASO, and less Stage 3 sleep on baseline PSG Shorter PSG total sleep duration and longer SOL predicted a greater improvement in insomnia (ISI) in the CBTi group alone (i.e., when the control group was excluded from the analysis). No other objective sleep parameters of quantitative PSG metrics predicted treatment-response to CBTi, versus control
Bensen-Boakes et al. (2022)	Sweetman et al. (2019b)	Investigate the effect of CBTi, versus control, on sleep state discrepancy (difference between PSG and self-reported sleep parameters) in patients with COMISA	Compared to no-treatment control, there was no effect of CBTi on changes in sleep state discrepancy metrics in patients with COMISA	N/A
Tu et al., (2022)	Ong et al. (2020)	Examine the impact of CBTi and PAP therapy versus PAP alone with self-monitoring for COMISA on nocturnal sleep, daytime functioning, and cognitive/emotional outcomes	Compared to PAP alone and self-monitoring, CBTi plus PAP resulted in greater reduction in dysfunctional sleep beliefs and more rapid improvements in functional sleepiness outcomes and fatigue symptoms	Younger participants had better self-reported SOL, lower WASO and better sleep efficiency than older people. Compared to married people, those who were not married had longer actigraphy SOL and WASO and shorter TST. Compared to moderate-to-severe OSA, participants with mild OSA had longer actigraphy TST and lower sleep diary sleep-quality

Abbreviations: AHI, apnoea–hypopnoea index; CBTi, cognitive behavioural therapy for insomnia; COMISA, comorbid insomnia and sleep apnoea; ISI, Insomnia Severity Index; N/A, not available; OSA, obstructive sleep apnoea; PAP, positive airway pressure; PSG, polysomnography; SOL, sleep onset latency; TST, total sleep time; WASO, wake after sleep onset.

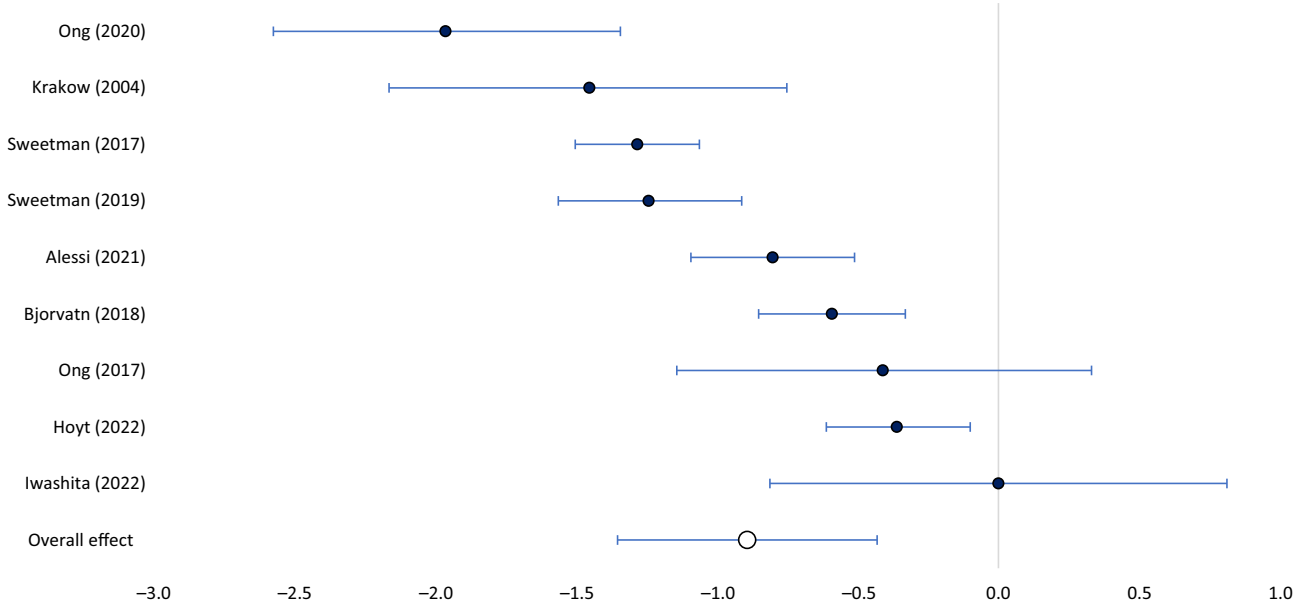

FIGURE 2 Overall Forest plot. [Color figure can be viewed at wileyonlinelibrary.com]

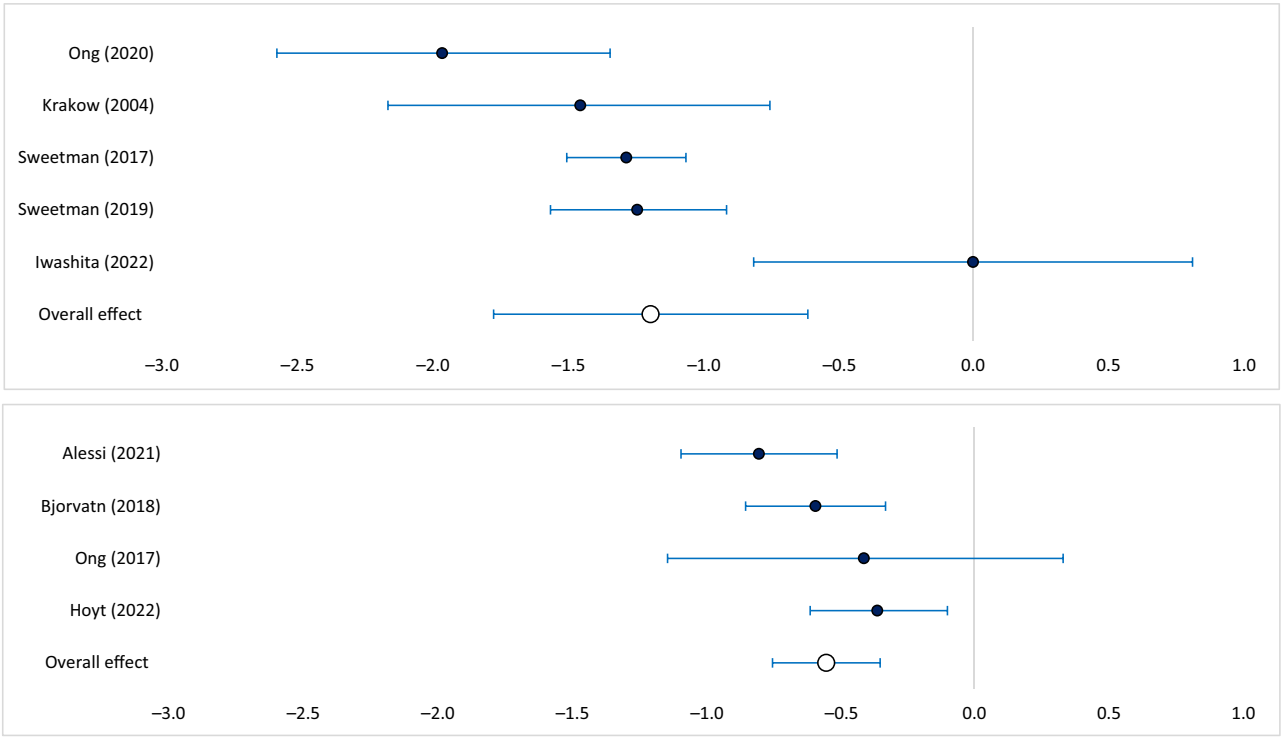

FIGURE 3 Forest plot of subgroup analyses for effect of cognitive behavioural therapy for insomnia (CBTi) in patients with untreated obstructive sleep apnoea (OSA) (top), and patients concurrently receiving treatment of OSA (bottom). [Color figure can be viewed at wileyonlinelibrary.com]

3.11 | Conference abstracts

Although not identified during the systematic literature search, there are several conference papers investigating the effect of CBTi in patients with COMISA that provided important foundational evidence in the field, and warrant discussion.

A conference abstract, Melendrez et al. (2001) described seven female crime victims with post-traumatic stress disorder and COMISA that were treated for nightmares and insomnia with sleep and dream behavioural therapies and CBTi, before commencing PAP therapy after a 3-month follow-up. Participants reported improvement in insomnia severity and overall sleep quality scores following

CBTi, and additional improvements following subsequent PAP therapy.

A conference abstract by Lack et al. (2003) reported on a case study of sleep restriction therapy in a patient with insomnia and previously undiagnosed OSA. Despite reporting an Epworth Sleepiness Scale score of zero, the patient had a minor motor-vehicle accident following the commencement of sleep restriction therapy. This case resulted in all patients in this specialist insomnia clinic being prospectively tested for comorbid OSA with home-based PSG and facilitated a subsequent RCT investigating the effect of CBTi on symptoms of daytime sleepiness in a larger cohort of patients with COMISA (Sweetman et al., 2020d).

A conference paper by Garland et al. (2016) reported on a four-arm RCT investigating the effect of CBTi + placebo, armodafinil alone, CBTi + armodafinil, or placebo-alone, on improving insomnia symptoms in 39 participants with COMISA commencing PAP therapy. CBTi was delivered by experienced therapists over eight 45–60 min sessions. Both CBTi groups showed significant and large reductions in the ISI (CBTi alone, $d = 3.44$; CBTi + armodafinil, $d = 3.56$). Insomnia remission (defined as a post-treatment ISI score of <7) was greater in the CBTi and CBTi + armodafinil groups (86% and 83%, respectively), compared to the armodafinil alone and placebo groups (33% and 22%, respectively).

A conference abstract by Lee et al. (2011) investigated the effect of a five-session CBTi programme in 36 patients with comorbid insomnia and mild-to-moderate OSA, versus 97 patients with insomnia alone. Overall improvements in diary-measured SOL, TST, and sleep efficiency were reported for both groups; however, the COMISA group completed treatment with lower self-reported sleep duration compared to those with insomnia alone.

A conference paper by Garb et al. (2012) reported on the effect of a group CBTi intervention, versus a booklet CBTi intervention in patients with insomnia alone, and insomnia comorbid with OSA and/or restless legs syndrome. Both interventions were associated with significant improvement in the ISI after treatment. There was a trend for greater improvement in diary-measured sleep efficiency in those with COMISA, compared to those without comorbid OSA.

Peters (2017) investigated the effectiveness of a sleep physician delivered CBTi programme in patients with insomnia alone ($n = 52$) and COMISA ($n = 147$). Non-response to CBTi (defined as final sleep efficiency <80%) was associated with presence of comorbid OSA, indicating a potential blunted response to CBTi in those with COMISA.

Edinger et al. (2015) investigated the effect of an online CBTi intervention, versus waitlist control, in 10 patients with COMISA currenting using PAP therapy. Although not statistically significant, the intervention group reported a greater mean ISI improvement (8-point reduction), compared to the waitlist group (3-point reduction). The intervention group reported a greater reduction in daytime sleepiness.

First, a study by Guilleminault et al. (2002) reported the effects of behavioural insomnia treatment, PAP therapy, and nasal turbinate surgery in 62 patients with upper airway resistance syndrome. This study was excluded as all participants had an AHI of <5 events/h sleep; however, warrants mention due to the specific focus on comorbid insomnia and breathing impairment during sleep. In all, 32 participants with comorbid insomnia and breathing impairment were allocated to immediate behavioural treatment for insomnia, consisting of six 90-min sessions including sleep hygiene information, sleep restriction therapy, stimulus control therapy and cognitive therapy. Participants showed improvements in actigraphy TST, PSG SOL, WASO and TST by 6-month follow-up.

Second, a protocol paper by Eldridge-Smith et al. (2022) describes a novel stepped-care CBTi trial among PAP-tolerant/treated patients with COMISA. Patients will be randomly allocated to a digital CBTi condition, versus sleep education control. Participants with persistent insomnia after 8 weeks will be re-randomised to continued online CBTi, or therapist-delivered CBTi. Initial data from this trial indicates a promising effect of digital CBTi, and feasibility of the stepped-care CBTi model in the management of PAP-treated patients with COMISA (Edinger, 2017). Future research should additionally investigate the effect of digital CBTi prior to initiation of PAP therapy in patients with COMISA, to determine the effect of digital CBTi on improving initial acceptance and use of PAP.

Five articles investigated the effect of CBTi in insomnia samples that incidentally included participants with comorbid OSA but did not report COMISA subgroup data. Authors were contacted to provide aggregate COMISA subgroup data. The Iwashita et al. (2022) data were provided, and thus included in the review and meta-analysis. However, COMISA subgroup data were unavailable or not provided for other studies, which were subsequently excluded from the systematic review.

Finally, a recent publication by Stahl et al. (2022) presenting two case studies of upper airway stimulation therapy in two patients with COMISA warrants discussion. The publication was excluded as few standardised otucome measures were reported. The first case was unable to use upper airway stimulation therapy due to comorbid insomnia symptoms. A four-session CBTi programme resulted in marked improvement in insomnia and subsequently improved adherence to the upper airway stimulation device at an amplitude required to control the OSA. The second case received a sequence of different treatments for both OSA and insomnia, which resulted in CBTi components being used to facilitate a reduction in eszopiclone use (and expected future discontinuation). These two cases highlight the numerous treatment options available for both insomnia and OSA that may be used in patients with COMISA. In addition to studies investigating CBTi and PAP therapy sequences in patients with COMISA, the efficacy and safety of non-PAP therapies and alternative treatments for insomnia should also be tested in patients with COMISA.

3.12 | Excluded records

Several publications that were screened but subsequently excluded from the systematic review also warrant discussion.

4 | DISCUSSION

The main finding of this systematic review and meta-analysis is that CBTi is associated with a large improvement in insomnia severity in

people with COMISA. CBTi improves insomnia when administered independently of PAP therapy, and concurrent with PAP therapy. These findings are based on 14 independent samples of 1040 patients with COMISA, including nine studies that were meta-analysed. The specific Hedges' g estimate of −0.89 should be interpreted with caution, given the large variability in study designs, interventions, sample characteristics, and effect sizes. Additional research is required to compare and confirm the effect of CBTi in patients with COMISA, including investigation of different CBTi modalities, treatment components, participant populations, and sequencing with OSA therapies. An additional seven studies reported on secondary outcomes and moderators of CBTi in patients with COMISA. Three of four recent RCTs comparing the combination of CBTi and PAP therapy, versus PAP alone, reported superior insomnia improvements in participants that received both CBTi and PAP therapy. Based on these data, it is recommended that patients with COMISA are treated with CBTi in addition to targeted management of OSA.

Previous meta-analyses have reported that CBTi is an effective treatment for insomnia, including in the presence of comorbid mental and physical health conditions (Geiger-Brown et al., 2015; Hertenstein et al., 2022; Morinet al., 1994; Wu et al., 2015). To our knowledge, this is the first systematic review and meta-analysis to specifically synthesise literature reporting on the effect of CBTi in patients with COMISA. Although there was variability between studies, with some reporting little effect of CBTi in patients with COMISA (Hoyt et al., 2022; Iwashita et al., 2022), the overall effect indicates a large improvement in insomnia among patients with both treated and untreated comorbid OSA. This large effect of CBTi on insomnia indicates that insomnia should not be viewed as a 'secondary symptom' of sleep apnoea in patients with COMISA. Although a sub-sample of patients with COMISA may experience respiratory events and arousals/awakenings that contribute to insomnia symptoms (Lundetræ et al., 2021; Sweetman et al., 2021b), the majority of patients with COMISA appear to be responsive to CBTi, which specifically targets the underlying psychological and behavioural factors known to perpetuate chronic insomnia. Until further data emerge to reliably identify patients with patterns of insomnia that is responsive to PAP therapy alone, it is recommended that all patients with COMISA should receive targeted assessment of both disorders, and that effective treatments for both insomnia and OSA should be made available.

This systematic review aimed to capture all peer-reviewed studies investigating the effect of CBTi in patients with COMISA, and consequently included a large variety of study designs. Due to the heterogeneity in study designs, care should be taken in directly comparing effect sizes from study-to-study. As seen in Figure 2, the two studies with 95% CIs that crossed the zero line were also the studies with the smallest sample sizes (Ong et al., 2017; Iwashita et al., 2022). This likely contributed to the overall heterogeneity of the included studies. Additionally, there was large variability in sample populations, length of intervention, specific interventions, eligibility criteria, outcome measures and follow-up periods from study-to-study. Unsurprisingly, this also resulted in a large range of scores on the Downs and Black study

TABLE 4 Research recommendations

1. Studies investigating the effect of CBTi in samples with insomnia frequently include incidental recruitment of participants with COMISA. To contribute to the limited information on the effects of CBTi in this population, simple treatment effects in the sub-sample of participants with COMISA should be reported.
2. Given the prevalence and morbidity of COMISA, but limited number of available studies, future research is needed to investigate and confirm the effects of CBTi in people with COMISA, and refine CBTi interventions for this population:
   a. Compare the effect of CBTi on insomnia symptoms in patients with treated versus untreated OSA.
   b. Compare the effect of CBTi on insomnia symptoms (and subsequent requirement for CPAP/CPAP adherence) in patients with an AHI ≥5 to <15, versus ≥15 events/h.
   c. Investigate the effectiveness of self-guided interactive online CBTi programmes, and hybrid online/clinician guided programmes in patients with COMISA (treated and untreated OSA).
   d. Investigate the effect of specific CBTi components (e.g., stimulus control therapy, sleep restriction therapy, relaxation therapy) on insomnia symptoms and PAP adherence outcomes in patients with COMISA.
   e. Conduct qualitative work with patients, to understand how CBTi can be further adapted to the management of COMISA.
   f. Systematic reporting of the following is recommended: adverse events and side-effects potentially associated with CBTi (e.g., headaches, daytime sleepiness, etc.), measures of treatment adherence (e.g., sessions completed, adherence to prescribed bedtime window), and descriptions of CBTi components (including sleep restriction therapy 'rules').
3. Implementation trials are necessary to translate evidence-based COMISA management pathways into sleep clinics that currently specialise in the diagnosis and management of OSA-alone. Conduct quantitative and qualitative assessments with clinicians, sleep technicians, and patients to understand the (cost) effectiveness, feasibility, and acceptability of embedding insomnia management pathways in sleep clinics.
4. Investigate the effect of digital CBTi in patients with COMISA. Compare the effectiveness and safety of digital CBTi in patients with treated and untreated OSA, and in patients with and without excessive daytime sleepiness.
5. Experimentally manipulate different sleep restriction therapy 'rules' in patients with COMISA to understand the best risk–benefit methods to improve insomnia symptoms while avoiding sleepiness-related adverse risks (e.g., initial restriction window, amount of incremental weekly adjustment of time in bed, etc.). Identify which patients with COMISA are most vulnerable to the effects of CBTi on increased daytime sleepiness and alertness failure due to sleep restriction therapy.
6. Investigate effect of CBTi on insomnia symptoms and PAP use in COMISA populations with specific insomnia subtypes (difficulties initiating sleep, maintaining sleep, early morning awakenings), and patients with/without pre-existing daytime sleepiness.

Abbreviations: CBTi, cognitive behavioural therapy for insomnia; COMISA, comorbid insomnia and sleep apnoea; PAP, positive airway pressure, OSA, obstructive sleep apnoea.

assessment checklist. Given the small number of studies, and high variability between studies in the area, further research is clearly required to confirm the effects of CBTi in patients with COMISA. The sections below provide several recommendations for future research in this area, and a summary is provided in Table 4.

4.1 | Adaptations to CBTi for COMISA

Future research should investigate adaptations to CBTi in patients with treated and untreated comorbid OSA. First, sleep restriction therapy (also *bedtime restriction therapy*) is one of the most effective treatment components of CBTi but can result in an acute increase in daytime sleepiness during the first 2–3 weeks of treatment (Sweetman et al., 2020d). Patients with COMISA may have higher levels of daytime sleepiness at baseline, and potentially an increased risk of sleepiness-related adverse events during the acute sleep restriction treatment phase (Lack et al., 2003). In an ancillary study to one of the RCTs (Ong et al., 2020), CBTi was associated with impairments in neurocognitive functioning (Turner et al., 2022). Consequently, it is recommended that clinicians monitor patients' levels of daytime sleepiness during each treatment session, and provide advice about management of alertness/sleepiness during the day to mitigate any accident risk (especially regarding sleepiness while driving or operating heavy machinery). It may be appropriate to consider a minimum prescribed bedtime window of 5.5–6 h instead of the 5-h minimum bedtime window often used in patients with insomnia alone, to further mitigate any sleepiness-related accident risk in patients with COMISA (Kyle et al., 2015). Future research should investigate self-reported and objective vigilance, alertness, and sleepiness parameters in patients with COMISA during sleep restriction therapy, to understand this risk profile. Furthermore, it may be possible to identify which patients with COMISA are most vulnerable to the acute effects of sleep restriction therapy on alertness failure, and adapt sleep restriction therapy algorithms accordingly (Kyle et al., 2014; Sweetman et al., 2020d; Vakulin et al., 2014).

Second, stimulus control therapy and sleep restriction therapy instructions may need to be modified in patients with COMISA that are using PAP therapy. For example, discussing expectations about the use (and removal) of PAP equipment during multiple sleep onset opportunities during the first nights of stimulus control therapy may be helpful to reduce frustration caused by removing/re-attaching PAP equipment (also see (Ong et al., 2017) for a description of the patients' lived experiences of concurrent treatment). Patients and PAP providers should also be aware of the possibility that sleep restriction therapy can result in an initial small reduction in TST during the first 1–2 weeks, which may also result in an overall reduction in nightly PAP use during this time. This might be particularly problematic for healthcare insurance reimbursement policies that are linked to arbitrary cut-offs for optimal PAP use. Although it is important to note that the majority of sleep restriction protocols set a minimum sleep window of 5 h (Kyle et al., 2015). Additionally, patients with untreated OSA who are expected to commence PAP therapy soon after CBTi could also be provided prospective guidance on the use of PAP therapy during ongoing sleep restriction titration, and future insomnia relapse prevention techniques.

Third, future research should investigate the prevalence and management of COMISA among different shift work populations including military personnel and first-responders (e.g., paramedics, fire-fighters, etc.). Sleep disorders are prevalent in shift workers, and management of insomnia with standardised CBTi protocols may have a blunted effect in this population (Reynolds et al., 2022). Adaptations to existing CBTi protocols, and incorporation of chronotherapies, changes to shift-scheduling, break times, and potentially hypnotic therapy may be required, depending on the nature, duration, and type of shift work/industry.

Importantly, CBTi adaptations for the COMISA population should be co-designed with input from patients, including those commencing treatment, and those that have completed CBTi programmes and trialled PAP therapy. Very few qualitative studies have been conducted in people with COMISA (Ong et al., 2017), to understand experiences and perceptions of the diagnosis, treatment, and ongoing care. This is important, given that assessment, diagnosis, and treatment of multiple sleep disorders is inherently more complex to patients.

4.2 | Effect of CBTi on PAP adherence

Patients with COMISA experience lower rates of PAP acceptance and use, compared to patients with OSA alone (Sweetman et al., 2021a). Therefore, several research groups have proposed that patients with COMISA should initially receive CBTi to improve insomnia symptoms and increase PAP acceptance and use. Although not the primary focus of this review, recent RCTs by Sweetman et al. (2019b) and Alessi et al. (2021) observed a significant increase in PAP adherence following CBTi, while Bjorvatn et al. (2018) and Ong et al. (2020) observed no effect of CBTi on PAP acceptance or use in patients with COMISA. Methodological differences between study samples and interventions may partially explain these different results.

First, the effect of CBTi on PAP use may depend on the specific CBTi modality and components that are used. For example, Bjorvatn et al. (2018) used a self-guided CBTi booklet intervention, while Sweetman et al. (2019b), Alessi et al. (2021), and Ong et al. (2020) used CBTi interventions delivered by trained clinicians/therapists. It is possible that patients with COMISA require tailored CBTi interventions from clinicians, rather than self-guided programmes without interactive features. At least two ongoing studies are investigating the effect of *interactive* digital CBTi programmes in patients with COMISA (Eldridge-Smith et al., 2022; Sweetman, 2022b). Future studies should compare the effectiveness of different CBTi modalities on improving insomnia and increasing PAP use in patients with COMISA (e.g., clinician-delivered, single-shot CBTi, interactive digital programe, blended/hybrid interventions). Furthermore, Alessi et al. (2021) used a combined CBTi and PAP adherence motivation enhancement intervention, making it difficult to identify the unique effect of CBTi alone

on improving PAP adherence. Although discrete interventions for insomnia and PAP adherence are useful in research studies to understand the unique effect of each intervention, the combined intervention used by Alessi et al. (2021) is likely a more suitable and effective model in clinical settings for improving clinical outcomes for patients with COMISA.

Second, the effect of CBTi on PAP adherence may depend on the specific OSA severity eligibility thresholds that are used in each study. For example, Sweetman et al. (2019b) and Alessi et al. (2021) used a threshold of at least moderate OSA, while Ong et al. (2020) included patients with mild, moderate, and severe OSA. Greater symptom improvement in OSA predicts greater PAP adherence and may be an important factor when identifying which patients with COMISA might benefit most from CBTi before commencing PAP therapy (i.e., those with more severe OSA at baseline are more likely to see improvements in their sleep after treatment). In a secondary analysis of RCT data, Sweetman et al. (2021c) also found that higher OSA severity predicted greater improvement of insomnia following CBTi, versus control. These results reinforce the potential importance of developing precision medicine approaches to improve assessment and tailored management of COMISA. Similarly, the effect of CBTi on PAP adherence (and motivation to use different treatments overall) may vary between studies that recruited participants from community populations (Ong et al., 2020), sleep clinic populations (Bjorvatn et al., 2018), and blended sample populations (Sweetman et al., 2019b).

In summary, the effect of CBTi on improving PAP adherence may be most pronounced in patients with at least moderate OSA, and when the CBTi intervention is delivered by trained clinicians, rather than through a static self-guided reading intervention. Future research should investigate the effectiveness of CBTi on PAP adherence in specific subgroups of patients with COMISA, and with a range of different CBTi modalities (e.g., brief four-session programmes, interactive online programmes, hybrid CBTi modalities including online/clinician components, etc.).

4.3 | Implementation of CBTi

Most sleep clinics worldwide currently specialise in the diagnosis and management of OSA alone. This likely contributes to suboptimal outcomes for the 30%–50% of patients with OSA with comorbid insomnia symptoms that are undiagnosed and would benefit from CBTi. It is important to consider implementation strategies to improve routine assessment of insomnia, and access and uptake of CBTi in patients with COMISA. Patient, clinician, and health system factors may impact the accessibility and uptake of CBTi in patients with COMISA.

Sleep clinic patients with COMISA may require education that insomnia and OSA are distinct co-occurring conditions that each require assessment and management approaches, to build expectations of the multi-faceted treatment pathway, and motivation to engage with different treatments for different disorders (Ong et al., 2017). The most effective sequence of treatments for insomnia and OSA is not definitively known, and should be based on patient preference, severity of each condition, and perceived value of initially treating insomnia to facilitate better uptake of PAP therapy (Sweetman et al., 2019a). Given that sleep restriction therapy is a difficult and unpleasant process for many patients, some patients with COMISA may benefit from specific motivational enhancement techniques to promote engagement with CBTi.

Second, despite consistent evidence that CBTi is effective in the presence of mental and physical health comorbidities (Sweetman et al., 2021d; Wu et al., 2015), conceptualisations of 'secondary insomnia' are pervasive throughout the health system and create a substantial barrier to CBTi access (Haycock et al., 2021). In the context of COMISA, it is likely that many clinicians view the OSA as the 'primary' condition and insomnia as the 'secondary' condition that will improve with PAP therapy. This conceptualisation would reduce the overall perceived value in referring a patient with COMISA for CBTi. Similarly, clinicians may consider that OSA is the condition associated with worse or more immediate physical health consequences (e.g., cardiovascular disease, Lechat et al., 2022a, 2022b), and expedite or prioritise management of the OSA before the insomnia. Education for primary care and specialist clinicians on COMISA, and the importance of targeted treatments for insomnia when comorbid with OSA is important to gradually change this persistent conceptualisation of 'secondary insomnia' and therefore increase access and use of CBTi. Indeed, CBTi not only improves insomnia, but has also been shown to reduce OSA severity (Sweetman et al., 2020d), and may increase subsequent adherence to PAP therapy in patients with COMISA (Sweetman et al., 2019a). Interestingly, waiting lists for PAP therapy can be long, and implementing CBTi between the diagnostic sleep study and PAP titration study/PAP initiation might be an optimal opportunity. As demonstrated in this systematic review, there is evidence that CBTi is safe and effective in patients with untreated OSA.

Third, significant issues in CBTi accessibility exist throughout the health system, especially in rural/remote areas, culturally and linguistically diverse populations, and minority groups, which contribute to the feasibility of those with COMISA (and insomnia alone) accessing CBTi. Of specific interest to COMISA, are the factors associated with CBTi access in sleep clinic settings, commercial PAP providers, and through remote OSA management services. The majority of sleep clinics worldwide currently specialise in the management of OSA alone, and do not include insomnia assessment or CBTi treatment/referral pathways. Future implementation trials should focus on new strategies to embed insomnia assessment pathways and CBTi treatment/referral mechanisms in these services.

For example, sleep clinics could include a brief self-report insomnia screening tool such as the ISI (Bastien et al., 2001) or Sleep Condition Indicator (Espie et al., 2014) in 'intake' questionnaires, to reliability identify patients in sleep clinic settings with insomnia symptoms. Such patients could be referred for CBTi programmes, including: manualised brief programmes, nurse-delivered programmes, or interactive online programmes. This would allow for CBTi to be administered between diagnostic appointments and subsequent PAP

commencement, without delaying PAP therapy. It is expected that this would contribute to improving insomnia symptoms, and potentially increasing subsequent acceptance and use of PAP therapy. Mixed-methods research to involve patient, staff, clinician, and health-system stakeholders is important to ensure that new models of care for COMISA are acceptable, effective, safe, and economically sustainable.

4.4 | Limitations

Although the present study has several strengths including prospective registration, reporting according to PRISMA standards, literature reviews, quality assessments, and data extraction by at least two independent authors, and meta-analyses of eligible studies with reporting of heterogeneity, it is not without limitations.

First, this review included studies with a large variety of study designs (e.g., single-arm studies, chart reviews, RCTs, case studies), samples with COMISA (e.g., insomnia clinic samples, sleep apnoea clinics, community recruited samples, military and veteran personnel), CBTi interventions (e.g., psychologist delivered, self-help booklet), and different insomnia outcome assessments and time-points. Although this broad inclusion criteria allowed for the systematic identification of the wide range of existing studies investigating the effect of CBTi in COMISA populations, care should be taken when directly comparing effect sizes from study-to-study. Similarly, the meta-analysis of studies investigating concurrent CBTi with PAP therapy was based on a small number of heterogenous studies and should be interpreted with caution. It is clear from the heterogeneity of CBTi interventions, COMISA samples, and outcome assessment measures that more research is needed to test and refine CBTi interventions for COMISA, identify the effectiveness of CBTi in people with COMISA recruited from different settings, and understand which symptoms of insomnia and OSA show the greatest treatment response to CBTi.

Second, the present review identified only 14 primary studies of 1040 participants with COMISA, of which nine studies were appropriate for meta-analysis. Although these studies indicate promising evidence for a large effect of CBTi on insomnia symptoms in patients with COMISA, more research investigating the effectiveness, safety, and limitations of CBTi in people with COMISA is essential. It may be possible to use existing datasets to contribute to this limited literature. For example, during the systematic review, we identified several studies that investigated incidentally included participants with COMISA among a larger sample of participants with insomnia. Most of these studies did not report the effect of CBTi among the sub-sample of participants with COMISA, as this was beyond the main scope of these studies. Unless comorbid OSA is a specific exclusion criterion in studies of participants with insomnia, future studies should expect that a substantial sub-sample of recruited participants with insomnia will have COMISA (e.g., approximately 30%–40% of those with insomnia; Sweetman et al., 2021b). Future clinical trials of CBTi that include sub-samples with insomnia alone and COMISA should compare (or report) outcome data between these groups to contribute to the limited existing literature reporting on the effect of CBTi in those with COMISA.

Third, our meta-analysis reported on the main effect of CBTi on insomnia symptoms and did not compare the effect of CBTi to control conditions. This is because we determined that there are presently too few RCTs investigating the effect of CBTi, versus control, on insomnia symptoms in the COMISA population to reliably meta-analyse. Consequently, it is likely that temporal effects, maturation effects, and non-specific treatment effects contributed to a small portion of the reported effect size of CBTi on insomnia symptoms in our meta-analysis. Additional RCTs investigating the effect of CBTi versus control in participants with COMISA are required to contribute to a reliable meta-analysis in the future.

Fourth, as this was not an individual participant-level data meta-analysis, we were not able to compare the effect of specific baseline sociodemographic (i.e., age, gender, BMI, race), sleep or daytime function characteristics on moderating treatment response to CBTi. Several secondary analyses of RCTs in participants with COMISA have investigate potential moderators of treatment response (i.e., Table 3); however, we were unable to quantitatively synthesise participant-level data in the present review. Future studies should aim to combine individual patient-level data from trials investigating the effects of CBTi in patients with COMISA to identify whether any characteristics predict which patients are more/less likely to respond to treatment.

Fifth, although this systematic review and meta-analysis focussed on changes in the ISI following CBTi, insomnia is also characterised by impairment in several nocturnal, cognitive, and daytime function domains that were not analysed. Several studies collected measures of sleep parameters (i.e., with sleep diaries, actigraphy and PSG), and self-reported daytime fatigue, sleepiness, depression, anxiety, and dysfunctional beliefs about sleep at pre- and post-treatment. However, we did not analyse the effect of CBTi on these secondary outcomes in our meta-analysis, as this was beyond the scope of the present review, and these outcomes were not consistently collected across enough different studies for reliable data synthesis. Future clinical trials of CBTi in patients with COMISA should collect sleep diaries, and measures of daytime sleepiness, fatigue, and mental health at each follow-up to facilitate a future meta-analysis of these effects.

4.5 | Conclusion

This systematic review and meta-analysis found that CBTi is an effective treatment for insomnia in patients with COMISA. Across 14 primary studies of 1040 participants, we found that CBTi resulted in a large improvement in insomnia (Hedges' $g = -0.89$). Subgroup analyses indicated that CBTi improves insomnia in patients with treated and untreated comorbid OSA. Based on these data, it is recommended that the 30%–50% of patients with OSA with COMISA are treated with CBTi to improve insomnia symptoms,

and potentially improve subsequent management of the comorbid OSA. Implementation programmes are required to improve access to CBTi for patients with COMISA in healthcare settings that have historically specialised in the management of OSA alone. Future research should aim to confirm the effects of CBTi in patients with treated and untreated OSA, identify subgroups of patients with COMISA that are most responsive to CBTi, and investigate the effectiveness of different CBTi modalities, delivery formats, and in specific COMISA patient populations.

AUTHOR CONTRIBUTIONS

All authors have approved this manuscript.

Alexander Sweetman: conceptualisation, drafting, draft search strategy, PROSPERO registration, systematic review screening, study quality assessment, data extraction.

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ACKNOWLEDGEMENTS

The authors report no funding for this review. The authors would like to thank and acknowledge Doctors Iwashita and Ong for supplying additional COMISA/CBTi subgroup data for this review and the University of Strathclyde librarian (Sarah Kevill) for support with the searches. Open access publishing facilitated by Flinders University, as part of the Wiley - Flinders University agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

Alexander Sweetman reports research funding support from the National Health and Medical Research Council (NHMRC), ResMed Foundation, Phillips, Flinders Foundation, and Flinders University, consultant work for Australian Doctor Group, SleepReviewMag, and Re-Time Australia. Douglas M Wallace reports consultancy work for Eisai and Idorsia. Megan Crawford is funded by Brain Research UK and is a consultant for Signifier Medical Technologies. The remaining authors report no relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

Authors will consider requests for systematic review and meta-analysis study data on reasonable request. Please contact authors of primary publications to enquire about access to de-identified participant-level data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sweetman, A., Farrell, S., Wallace, D. M., & Crawford, M. (2023). The effect of cognitive behavioural therapy for insomnia in people with comorbid insomnia and sleep apnoea: A systematic review and meta-analysis. *Journal of Sleep Research*, *32*(6), e13847. https://doi.org/10.1111/jsr.13847