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CLINICAL REVIEW

Cognitive behavioral therapy for insomnia in patients with mental disorders and comorbid insomnia: A systematic review and meta-analysis

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SUMMARY

Almost 70% of patients with mental disorders report sleep difficulties and 30% fulfill the criteria for insomnia disorder. Cognitive behavioral therapy for insomnia (CBT-I) is the first-line treatment for insomnia according to current treatment guidelines. Despite this circumstance, insomnia is frequently treated only pharmacologically especially in patients with mental disorders. The aim of the present meta-analysis was to quantify the effects of CBT-I in patients with mental disorders and comorbid insomnia on two outcome parameters: the severity of insomnia and mental health.

The databases PubMed, CINHAL (Ebsco) und PsycINFO (Ovid) were searched for randomized controlled trials on adult patients with comorbid insomnia and any mental disorder comparing CBT-I to placebo, waitlist or treatment as usual using self-rating questionnaires as outcomes for either insomnia or mental health or both. The search resulted in 1994 records after duplicate removal of which 22 fulfilled the inclusion criteria and were included for the meta-analysis. The comorbidities were depression (eight studies, 491 patients), post-traumatic stress disorder (PTSD, four studies, 216 patients), alcohol dependency (three studies, 79 patients), bipolar disorder (one study, 58 patients), psychosis (one study, 50 patients) and mixed comorbidities within one study (five studies, 189 patients). The effect sizes for the reduction of insomnia severity post treatment were 0.5 (confidence interval, CI, 0.3–0.8) for patients with depression, 1.5 (CI 1.0–1.9) for patients with PTSD, 1.4 (CI 0.9–1.9) for patients with alcohol dependency, 1.2 (CI 0.8–1.7) for patients with psychosis/bipolar disorder, and 0.8 (CI 0.1–1.6) for patients with mixed comorbidities. Effect sizes for the reduction of insomnia severity were moderate to large at follow-up. Regarding the effects on comorbid symptom severity, effect sizes directly after treatment were 0.5 (CI 0.1–0.8) for depression, 1.3 (CI 0.6–1.9) for PTSD, 0.9 (CI 0.3–1.4) for alcohol dependency in only one study, 0.3 (CI −0.1 – 0.7, insignificant) for psychosis/bipolar, and 0.8 (CI 0.1–1.5) for mixed comorbidities. There were no significant effects on comorbid symptoms at follow-up.

Together, these significant, stable medium to large effects indicate that CBT-I is an effective treatment for patients with insomnia and a comorbid mental disorder, especially depression, PTSD and alcohol dependency. CBT-I is also an effective add-on treatment with the aim of improving mental health in patients with depression, PTSD, and symptom severity in outpatients with mixed diagnoses. Thus, in

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patients with mental disorders and comorbid insomnia, given the many side effects of medication, CBT-I should be considered as a first-line treatment.

Introduction

Insomnia is a sleep disorder characterized by sleep onset and/or sleep maintenance difficulties and daytime impairment such as tiredness, reduced concentration or excessive worry about sleep [1]. Of individuals with mental disorders, almost 70% report sleep onset or sleep maintenance problems and over 30% fulfill the criteria for insomnia disorder according to the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) [1]. Patients with comorbid insomnia, compared to those suffering from a mental disorder without insomnia, are characterized by a more adverse course of the mental disorder and lower general treatment efficacy [1]. A diagnosis of insomnia increases the probability of de novo onset of major depressive disorder and other mental disorders [2,3]. In patients with depression, insomnia and nightmares increase the risk of suicidal ideation, suicide attempts and completed suicides [4].

According to the international classification of diseases, 10th edition (ICD-10), insomnia is a symptom of many somatic and mental disorders and should only be classified as a separate diagnosis when dominating the clinical picture [5]. In terms of treatment indication, this means that treatment of the mental disorder would often be sufficient and disorder-specific treatment of insomnia would not be necessary. Research, however, has demonstrated that on the contrary, insomnia often persists despite successful antidepressant treatment and increases the risk of a relapse into depression [6]. Absence of insomnia after successful antidepressant treatment is a predictor for the restoration of a normal level of functioning [6]. In DSM-5, insomnia disorder can be given as a single diagnosis or as a comorbidity to any mental disorder [7]. Specifiers (extensions with further explanations to a diagnosis) are used to indicate whether comorbidity is present. Clinical judgment, which takes into account the course, severity and presentation of both insomnia and the comorbid mental disorder is necessary to decide whether a coexisting mental disorder fully explains the insomnia complaint or whether insomnia is an independent diagnosis.

Cognitive behavioral therapy for insomnia (CBT-I) is a multicomponent treatment including sleep education, behavioral interventions such as bedtime restriction and stimulus control, relaxation and cognitive therapy [8]. In patients with insomnia without psychiatric comorbidity, CBT-I is highly effective for the improvement of self-rated insomnia severity and several other sleep parameters like for example sleep onset latency and wake time after sleep onset [9], including daytime symptoms [10]. CBT-I is also feasible and effective when delivered via the internet [11].

CBT-I has been adapted with the aim of addressing the needs of patients with different mental disorders. Examples for adaptations are the inclusion of treatment components for nightmares in patients with post-traumatic stress disorder (PTSD) [12], techniques to overcome sleep inertia for patients with bipolar disorder [13], and chronobiological treatment components for patients with attention deficit hyperactivity disorder (ADHD) [14]. Using a transdiagnostic approach, CBT-I has recently been adapted for patients with severe mental disorders during acute psychiatric inpatient treatment [15,16].

In their meta-analysis, Wu and colleagues found that CBT-I was more effective for patients with mental comorbidity compared to medical comorbidity [17]. Since their meta-analysis including nine primary studies was conducted, a relevant number of new randomized controlled trials in this patient group has been added, calling for a reassessment of effects. Focusing on comorbid depression and insomnia in their meta-analysis, Gee et al. concluded that non-pharmacological treatment for insomnia is effective not only for the reduction of insomnia, but has moderate to large effects on depression especially in clinical populations [18]. A recent meta-analysis concluded that sleep improvement after different non-pharmacological treatments for insomnia is causally related to improvements in mental health [19].

The aim of the present meta-analysis was to focus on CBT-I, the recommended first-line treatment for insomnia, and quantify its effect on insomnia severity and mental health, in patients with all mental disorders. With our focus on comorbid insomnia, we target two aspects that are to date under-investigated: the effect of CBT-I on comorbid symptoms (beyond insomnia), and the differential effects of CBT-I in subgroups of patients with different mental disorders.

Methods

This literature review and meta-analysis has been conducted in accordance with the recommendations of reporting for meta-analyses of observational studies in epidemiology (MOOSE) and the PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions [20,21]. This meta-analysis has been registered with PROSPERO with the registration number CRD42021249929. The methodological approach differs from the Prospero registration because adaptations have been made during the review process. In contrast to a between-group comparison of pre-post differences (registered on Prospero), the final analysis is based on a between-group comparison of the post treatment values. This modification reflects a statistical re-evaluation across the review process. As stated, comparing the post treatment means only, instead of a change score between baseline and post means, is less prone to bias [22].

Search strategy

Three authors (EH, ET, TS) were involved in literature search, abstract screening, full-text screening, and data extraction for the included studies. Studies were reviewed by two independent raters. Discrepancies were discussed and solved in consensus with the co-authors. The literature search was done using the databases PubMed, CINHAL (Ebsco) und PsycINFO (Ovid).

The final search was conducted in October 2021. A search period of 1980 until October 2021 was set according to the publication of the DSM III in 1980, formulating the first set of modern definitions of mental disorders and insomnia [23]. The search strategy consisted of 79 search terms for different mental disorders and syndromes, in conjunction with search terms for sleep problems and search terms for CBT-I. The full search strategy is provided in Appendix S1. Reference lists of included publications were screened for additional potentially eligible studies. Moreover, sleep researchers from the European Insomnia Network were contacted via e-mail to ask for unpublished and ongoing studies on the topic.

Study selection

We formulated the following inclusion and exclusion criteria for primary studies with the aim of including high quality clinical trials allowing conclusions regarding the efficacy of CBT-I in patients with insomnia and comorbid mental disorders:

- **Date**: All included studies had to be published between 1980 (publication date of the DSM III) and October 2021.
- **Language**: Studies had to be published in English, German, Italian, French or Swedish (languages proficiency of authors.)
- **Type of publication**: Only original studies were included. Reviews, other meta-analyses, comments, book chapters and dissertations were not eligible.
- **Study design**: Only randomized controlled trials were included.
- **Age**: Study participants had to be 18 y or older.
- **Diagnosis**: Diagnosis of insomnia and the mental disorder had to be based on a version of DSM (DSM III or higher) or ICD or the International Classification of sleep disorders (ICSD) for insomnia or an abnormal score, exceeding the cutoff for pathology, in a validated self-rating questionnaire.
- **Outcome variables**: The severity of insomnia and the mental disorder had to be assessed with validated self-rating questionnaires (not sleep diaries only). For insomnia, polysomnographic results without questionnaire results were not eligible.
- **Intervention**: A behavioral treatment component of CBT-I (either sleep restriction or stimulus control) was mandatory for inclusion into this meta-analysis because sleep restriction has been identified as an effective stand-alone treatment for insomnia [24] and stimulus control was identified as an effective component of CBT-I [25–27]. Other CBT-I components such as relaxation training, sleep education, and cognitive therapy could be included but were not mandatory. CBT-I could be delivered face-to-face or remotely. CBT-I could be combined with disorder-specific treatment of the mental disorder if the study included a group receiving this same treatment without CBT-I. We also included studies investigating a modified version of CBT-I for patients with mental disorders, e.g., treatment packages including CBT-I plus treatment for nightmares or CBT-I plus treatment for circadian disruption.
- **Control group**: Each study had to include a control group receiving no treatment, placebo, waitlist or treatment as usual without specific sleep treatment. Studies only comparing two different sleep interventions were not eligible.

Data extraction

The following variables were manually extracted from all included studies: authors and year of publication, number of participants in each group at baseline, post-treatment and follow-up(s), age of participants at baseline, percentage of females at baseline, number of follow-up measurements, time between baseline and each follow-up, diagnostic approach for insomnia and the mental disorder, therapeutic techniques used in CBT-I, number of sessions, description of the control conditions, mean and standard deviation for the severity of insomnia and the mental disorder at baseline, post-treatment and follow-up(s). The Insomnia Severity Index (ISI) was chosen as a measure of insomnia severity if available because it is a well-known, validated questionnaire that is sensitive to change [28].

The authors of four included studies were contacted and asked for additional data as the data provided in their publications did not allow for the calculations necessary for this meta-analysis. Three of four provided the necessary data. The remaining study was excluded.

Meta-analytic calculations

Meta-analyses quantifying the standardized mean difference in the CBT-I group versus the control condition were calculated for insomnia severity and mental health for post treatment and first follow-up. Where available, means of intention-to-treat analyses were included instead of completer data.

The statistics software R was used for meta-analytic calculations. We used the R package *Metafor* [29]. As a measure of effect size, Hedges' g was calculated as the difference between the post (follow-up) mean of the treatment group and the control group, divided by the pooled standard deviation. Hedges' g of >0.8 can be interpreted as a large effect, Hedges' g between 0.5 and 0.8 indicates a medium effect, and Hedges'g between 0.2 and 0.5 indicates a small effect. Calculating effect size with the post (follow-up) means only, instead of a change score between baseline and post (follow-up) means, is less prone to bias, whereas a potential between-group difference in baseline scores does not necessarily lead to biased results [22].

Assuming that there is a distribution of true effect sizes rather than a single true effect size, a random-effects model was selected for meta-analytic pooling of the primary studies as recommended by Borenstein et al. [30]. I^2 was used as an indicator of between-study heterogeneity. I^2 describes the proportion of total variation in the estimated effect sizes that is due to heterogeneity among studies [31]. An I^2 of 50% or larger is commonly understood as an indicator of heterogeneity. Only in absence of heterogeneity, it is recommended to use the fixed effects model, as it assumes that all studies share a common true effect size [30].

Assessment of risk of bias

The Cochrane Risk of Bias Tool (RoB) was used to estimate the risk of bias in the included studies. The tool is, among others, recommended for estimating risk of bias in RCTs and considered superior to e.g., the Jadad Scale or the Delphi List [32]. With the RoB, risk of bias in individual RCTs can be estimated in five different domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. A summary category (low, moderate or high risk of bias) was estimated for each primary study using the Cochrane excel cribsheet that can be found on the website riskofbias.info [33]. Risk of bias ratings were performed by ET and TS supervised by EH. Inconsistencies were discussed and agreed upon among the authors. Two studies were rated by both ET and TS and resulted in the same overall risk of bias rating.

Publication bias

Visual inspection of funnel plots and Egger's tests were used to estimate publication bias [34]. Funnel plots and Egger's test are based on a comparison of the effect size against the standard error.

Results

Study flow

The flow of primary studies from electronic search, screening for eligibility and inclusion is shown in Fig. 1, following and adopted

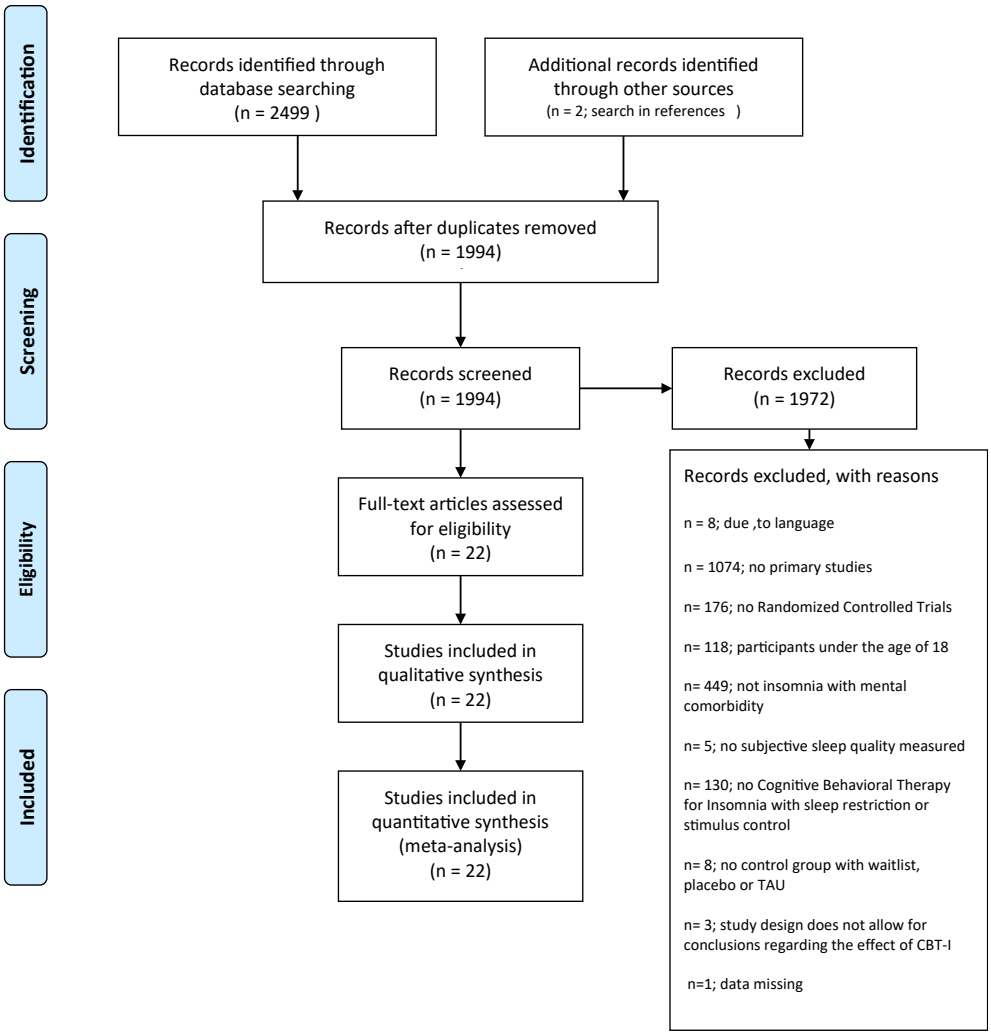

Fig. 1. Study flow.

from the PRISMA guidelines [20]. The search resulted in 1994 hits after duplicate removal. We included n = 22 primary RCTs into the meta-analysis.

Description of the study sample

The 22 primary studies are described in Table 1. The comorbid mental disorders in the included primary studies were depression (8 studies), PTSD (4 studies), alcohol dependency (3 studies), bipolar disorder (1 study), psychosis (1 study) and mixed comorbidities within one study (5 studies). The participants were middle-aged to older adults – the mean age in the study with the youngest sample was 34.1 ± 10.8 [35], the oldest sample was on average 74.7 ± 7.1 years old [36]. All but three studies reported the ISI as an outcome for insomnia severity. Where available, the ISI was chosen for meta-analytic calculations. The three remaining studies used the Pittsburgh Sleep Quality Index [37].

The outcome measure for mental health were heterogeneous due to the heterogeneity of the mental disorders themselves and due to different instruments chosen to assess the same mental disorder in the individual primary studies. Several primary studies reported more than one potentially eligible outcome measure of the effect. Where available, we chose a disorder-specific outcome (e.g., a rating scale for depression severity rather than a wellbeing-scale for a study with patients with depression). However, for the studies with mixed mental comorbidity, we chose the general outcome measure of wellbeing/quality of life for meta-analytic calculations. For one study in patients with alcohol dependency, we chose the Beck Depression Inventory because a specific measure of the severity of alcohol dependency was not available [38].

Twenty out of 22 studies investigated a treatment package including behavioral treatment, cognitive restructuring and relaxation. The two remaining studies used brief behavioral treatment including only behavioral treatment components (sleep restriction and stimulus control) [39,40]. Details regarding the intervention in each included trial can be found in Supplementary Table 1. Several studies included add-on components in addition to CBT-I. These were imagery rehearsal therapy for nightmares [41,42], rise routines and light therapy [15], and adaptations for a specific comorbid disorder [36,43].

The number of sessions ranged from one (plus one telephone-based session) to eight. CBT-I was delivered as face-to-face individual therapy in 20 trials. The other two trials delivered CBT-I online (one study) or in a group format (one study). In 12 studies, CBT-I was combined with some form of treatment for the mental disorder. This comprised different forms of treatment from unstandardized "treatment as usual" to inpatient psychiatric care. In these 12 studies, the control group received the same treatment for the mental disorder without CBT-I. In the trials without study-specific treatment for the mental disorder, the control groups

Table 1
Characteristics of the included primary studies. BDI, Beck Depression Inventory; CBT-I, Cognitive Behavioral Therapy for Insomnia; CES-D, Centre for Epidemiological Studies Depression Scale; GRID HAMD, Grid Hamilton Rating Scale for Depression; HAMD, Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptomatology; ISI, Insomnia Severity Index; PANSS, Positive and Negative Syndrome Scale; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; PTSD post-traumatic stress disorder; SF-36, Short Form Health Questionnaire 36; TAU, treatment as usual; WEMWBS, Warwick–Edinburgh Mental Wellbeing Scale.

Author	Country	N	Age (treatment group)	% females	Comorbidity	Outcome comorbidity	Outcome insomnia	FU1	FU2	Treatment group	Control group
Arnedt et al., 2011 [46]	USA	17	46.2 ± 8.9	35.29%	Alcohol	Time Line Follow Back abstinent days	ISI	None	None	CBT-I adapted for patients with alcohol dependency, individual, eight sessions	Behavioral placebo
Ashworth et al., 2015 [47]	Australia	42	37.1 ± 12.8	61%	Depression	BDI II	ISI	3 mo	None	CBT-I, individual, four sessions	Written self-help
Carney et al., 2017 [48]	USA & Canada	71	44.97 ± 9.38	68%	Depression	HAMD 17	ISI	6 mo	None	CBT-I, individual, four sessions + escitalopram	Escitalopram + sleep hygiene
Chakravorty et al., 2019 [49]	USA	22	52 ± 7	0%	Alcohol	Penn Alcohol Craving Scale	ISI	3 mo	6 mo	CBT-I, individual, eight sessions	Monitoring
Currie et al., 2004 [38]	Canada	40	43.3 ± 10.9	30%	Alcohol	BDI	PSQI	3 mo	None	CBT-I, individual, five sessions	Waitlist, sleep diary
Edinger et al., 2009 [50]	USA	41	52 ± 11.1	15%	Mixed	None	PSQI	6 mo	None	CBT-I, individual, four sessions	Sleep education
Freeman et al., 2015 [44]	UK	50	39.6 ± 11.6	32%	Psychosis	PANSS total score	ISI	3 mo	None	CBT-I, individual, eight sessions + standard care	Standard care
Glozier et al., 2019 [51]	Australia	87	58.6 ± 6.3	0%	Depression	CES-D	ISI	6 mo	None	CBT-I, online, six sessions	Online sleep education
Harvey et al., 2015 [52]	USA	58	37.7 ± 12.4	62%	Bipolar	IDS-C	ISI	6 mo	None	CBT-I adapted for bipolar patients, individual, eight sessions	Psychoeducation
Manber et al., 2008 [53]	USA	30	49.5 ± 13.6	61%	Depression	HDRS 17 without sleep items	ISI	None	None	CBT-I, individual, seven sessions + 12 wk of escitalopram	Quasi-desensitization + 12 wk of escitalopram
Manber et al., 2016 [54]	USA	150	46.6 ± 12.6	73.34%	Depression	HDRS	ISI	4 mo	None	Depression pharmacotherapy + CBT-I, individual seven sessions	Depression pharmacotherapy + control therapy for insomnia
Ochsner Margolies et al., 2013 [41]	USA	40	36.4 ± 9.3	10%	PTSD	PTSD symptom scale	ISI	None	None	CBT-I, individual, four sessions	Waitlist
Pigeon et al., 2017 [55]	USA	27	56.9 ± 10	11%	Depression	PHQ-9 without sleep items	ISI	3 mo	None	brief behavior therapy, individual, two face-to-face sessions and two telephone calls	Sleep education
Pigeon et al., 2019 [56]	USA	54	52.8 ± 14.5	20%	Depression and PTSD	Columbia suicide severity rating scale	ISI	None	None	CBT-I, individual or telehealth, four sessions + TAU	TAU (not standardized)

(*continued on next page*)

Table 1 (*continued*)

Author	Country	N	Age (treatment group)	% females	Comorbidity	Outcome comorbidity	Outcome insomnia	FU1	FU2	Treatment group	Control group
Pigeon et al., 2021 [35]	USA	110	34.21 ± 10.81	97.3%	PTSD	Clinician-administered PTSD scale (CAPS)	ISI	5 mo	None	4 weekly sessions of CBT-I+ 12 weekly sessions of CPT over 20 wk	Control calls + 12 weekly sessions of CPT over 20 wk
Sadler et al., 2018 [36]	Australia	47	74.7 ± 7.1	52%	Depression	Geriatric depression scale	ISI	3 mo	None	CBT-I, group, eight sessions	Psychoeducation
Sheaves et al., 2018 [45]	UK	40	40 ± 12	0%	Mixed	WEMWBS	ISI	2 wk	10 wk	CBT-I, individual, minimum five sessions, plus standard care in psychiatric hospital	Standard care in psychiatric hospital
Talbot et al., 2014 [57]	USA	45	37.1 ± 10.4	69%	PTSD	PTSD checklist (without sleep items)	ISI	None	None	CBT-I, individual, eight sessions + TAU for PTSD (pharmacotherapy or psychotherapy)	Waitlist, sleep diary + TAU for PTSD (pharmacotherapy or psychotherapy)
Taylor et al., 2015 [58]	USA	23	50.1 ± 13.1	89%	Mixed	SF-36 mental component score	ISI	None	None	CBT-I, individual, threesessions in person and two telephone calls + TAU in outpatient clinic	TAU in outpatient clinic
Ulmer et al., 2011 [42]	USA	21	47 ± 9.47	39%	PTSD	PTSD checklist military version	ISI	None	None	CBT-I plus Imagery Rehearsal, individual, six sessions + TAU by primary care providers	TAU by primary care providers
Wagley et al., 2013 [39]	USA	31	43.6 ± n.r.	70%	Mixed	PHQ-9	PSQI	1 mo	None	Brief behavior therapy, individual, one session and one telephone call + TAU in outpatient clinic	TAU in outpatient clinic
Watanabe et al., 2012 [40]	Japan	37	52.9 ± 11.6	62.20%	Depression	GRID HAMD (without sleep items)	ISI	2 mo	None	Brief behavior therapy, individual, four sessions TAU	TAU

were allocated either to a waitlist, monitoring, self-help, education or behavioral placebo. We did not include studies were CBT-I was only compared to another treatment with potential efficacy for insomnia (e.g., comparison of two different forms of CBT-I), as such studies would not be comparable to the rest of our sample in terms of effect size.

Six out of 22 studies reported on adverse events related to CBT-I. All of these six state that no adverse events related to the intervention had been observed. The authors of the remaining 14 articles do not report whether adverse events were observed. Serious adverse events were reported by Freeman et al. in patients with psychosis [44] and Sheaves et al. in psychiatric inpatients [45]. The events were suicide attempts and violent incidents. All serious adverse events were considered unrelated to the study intervention.

Main results

The main results of the meta-analysis are summarized in Figs. 2–5. For the severity of insomnia post treatment, we found a large effect favoring CBT-I (Hedges' g 1.0, CI 0.7–1.2). Twelve studies reported data on the severity of insomnia at first follow-up. The first follow-up was between two weeks and six months after the end of treatment. We found a large effect favoring CBT-I at first follow-up (Hedges' g 0.8, CI 0.4–1.2). Only two studies reported

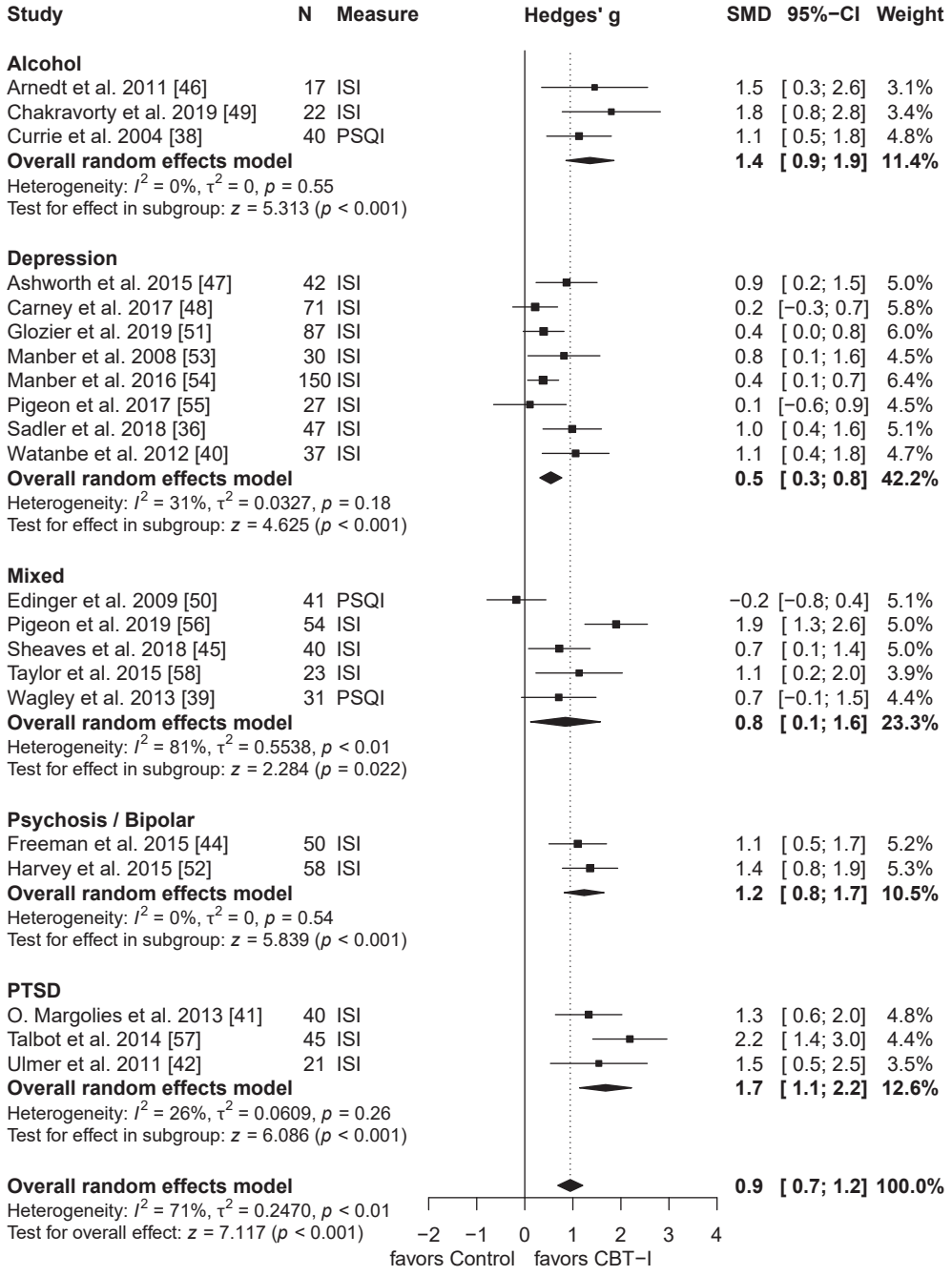

Fig. 2. Severity of Insomnia post treatment. ISI, insomnia severity index; PSQI, Pittsburgh sleep quality index. N, sample size (total sample).

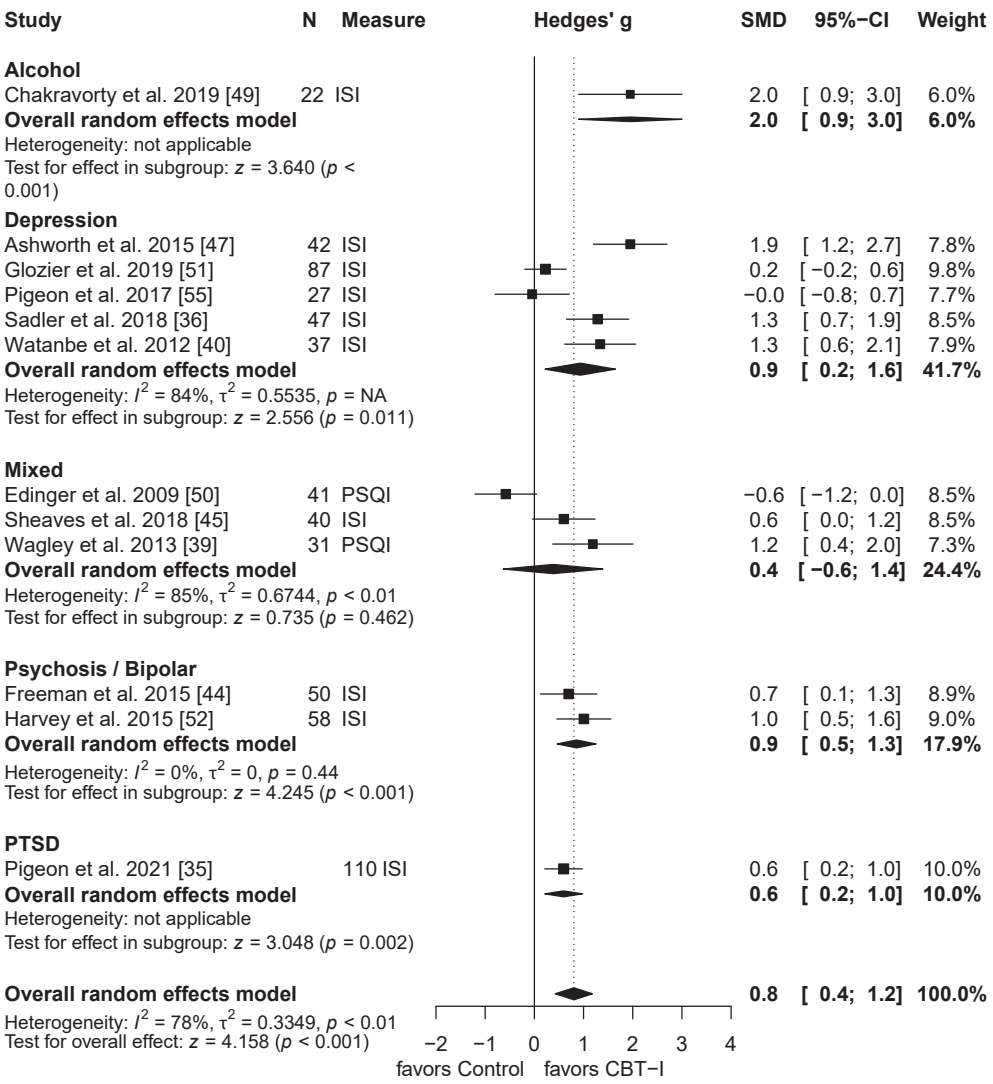

Fig. 3. Severity of Insomnia at follow-up. ISI, insomnia severity index; PSQI, Pittsburgh Sleep Quality Index. N, sample size (total sample).

data on the severity of insomnia at second follow-up. Therefore, no meta-analysis was calculated for the second follow-up.

Twenty-one primary studies reported data for mental health at post-treatment. We found a moderate effect favoring CBT-I (Hedges' g 0.7, CI 0.4–0.9). Eleven studies reported data on mental health at first follow-up. We found a moderate effect favoring CBT-I (Hedges g 0.5, CI 0.2–0.7).

To further specify the efficacy of CBT-I for patients with different mental disorders, we divided the total sample of 22 studies into five subgroups: depression (8 studies), PTSD (4 studies), alcohol dependency (3 studies), psychosis and bipolar disorder (2 studies), and mixed comorbidities within the study sample (5 studies). For the severity of insomnia post treatment, the effect was significant with a large effect size in alcohol dependency, mixed comorbidity, psychosis/bipolar, and PTSD and significant with a moderate effect size for depression. For the severity of insomnia at follow-up, the effect was significant with a large effect size for alcohol dependency, depression, and psychosis/bipolar, but insignificant for the mixed subgroup. There was only one study reporting on PTSD at follow-up. For mental health post treatment, the effect was significant with a large effect size for alcohol dependency, mixed comorbidity, and PTSD. The effect was significant with a moderate effect size for depression and non-significant for psychosis/bipolar. For mental health at follow-up, the effect was not significant for any subgroup and effect sizes were small to moderate.

The results of the meta analyses for the total sample and the subgroups are shown in Figs. 2–5.

The I^2 statistic indicated a high amount of heterogeneity (over 50%) in the total sample at both time points and for both outcomes Heterogeneity was still significant within the depression subgroup and within the mixed subgroup (Figs. 2–5).

Risk of bias

The risk of bias for the individual primary studies is summarized in Fig. 6. The overall risk of bias was low for five studies, high for four studies and moderate for remaining 13 studies. Important sources of risk of bias in the primary studies were missing data due to dropouts throughout the pre-post-follow-up designs and the fact that true blinding is often not possible in psychotherapy studies, constituting a risk of bias concerning the measurement of the outcome. With self-rating questionnaires as primary outcomes, the belief of having been in the intervention group/control group may have an influence on the outcome.

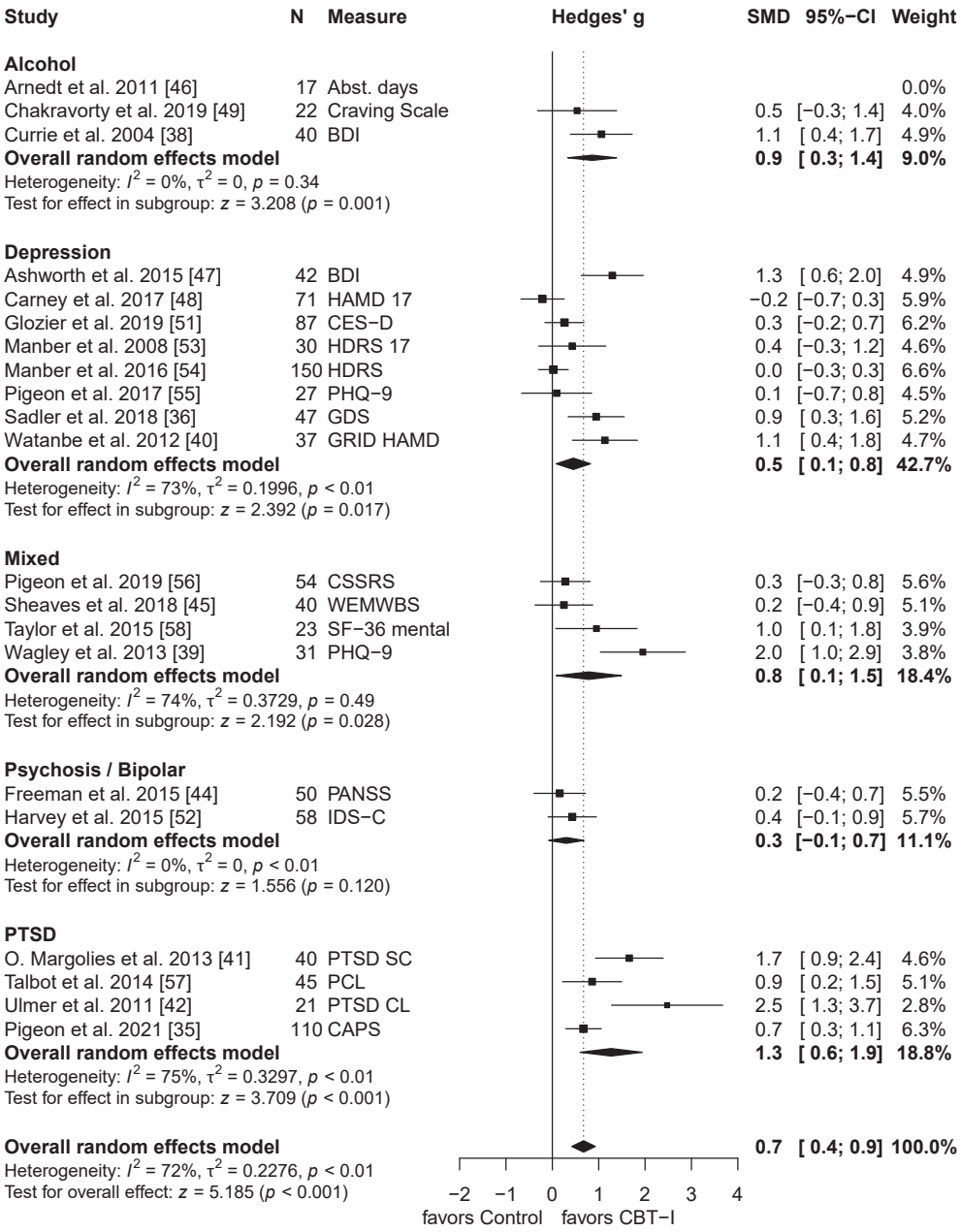

Fig. 4. Mental health post treatment. BDI, Beck Depression Inventory; CES-D, centre for epidemiological studies depression scale; GRID HAMD, Grid Hamilton Rating Scale for Depression; HAMD, Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptomatology; PANSS, Positive and Negative Syndrome Scale; PCL, PTSD checklist; PHQ, Patient Health Questionnaire; SF-36, Short Form Health Questionnaire 36; WEMWBS, Warwick–Edinburgh Mental Wellbeing Scale. N, sample size (total sample).

Publication bias

The Egger test for funnel plot asymmetry was performed as an indicator of publication bias [30]. The Egger test was significant for insomnia and for comorbidity post treatment, indicating potential publication bias (insomnia: $t = 2.59$, $df = 20$, $p = 0.017$; comorbidity: $t = 3.92$, $df = 18$, $p = 0.001$). Egger tests were non-significant ($p > 0.1$) for insomnia and comorbidity at follow-up. Funnel plots are shown in the appendix.

Discussion

This meta-analysis found that in patients with a mental disorder and comorbid insomnia, CBT-I is significantly more effective than control conditions both for the reduction of insomnia and the improvement of mental health. We found large effect sizes for the reduction of the severity of insomnia both directly after treatment and at first follow-up (3–6 mo after end of treatment for most studies) and moderate effect sizes for the improvement of mental health post-treatment. More specifically, a significant improvement of alcohol dependency, depression, mixed comorbidity and PTSD, but not psychosis and bipolar disorder was observed directly after treatment, but not at follow-up.

We can only speculate why effect sizes for mental health in the disorder-specific subgroups did not reach significance any more at follow-up. Effect sizes decreased from post-treatment to follow-up for both insomnia and mental health. This is a commonly observed effect, most likely because strategies implemented throughout the course of therapy are not used by the patients any more with time passing. Whereas effect sizes were generally larger for insomnia

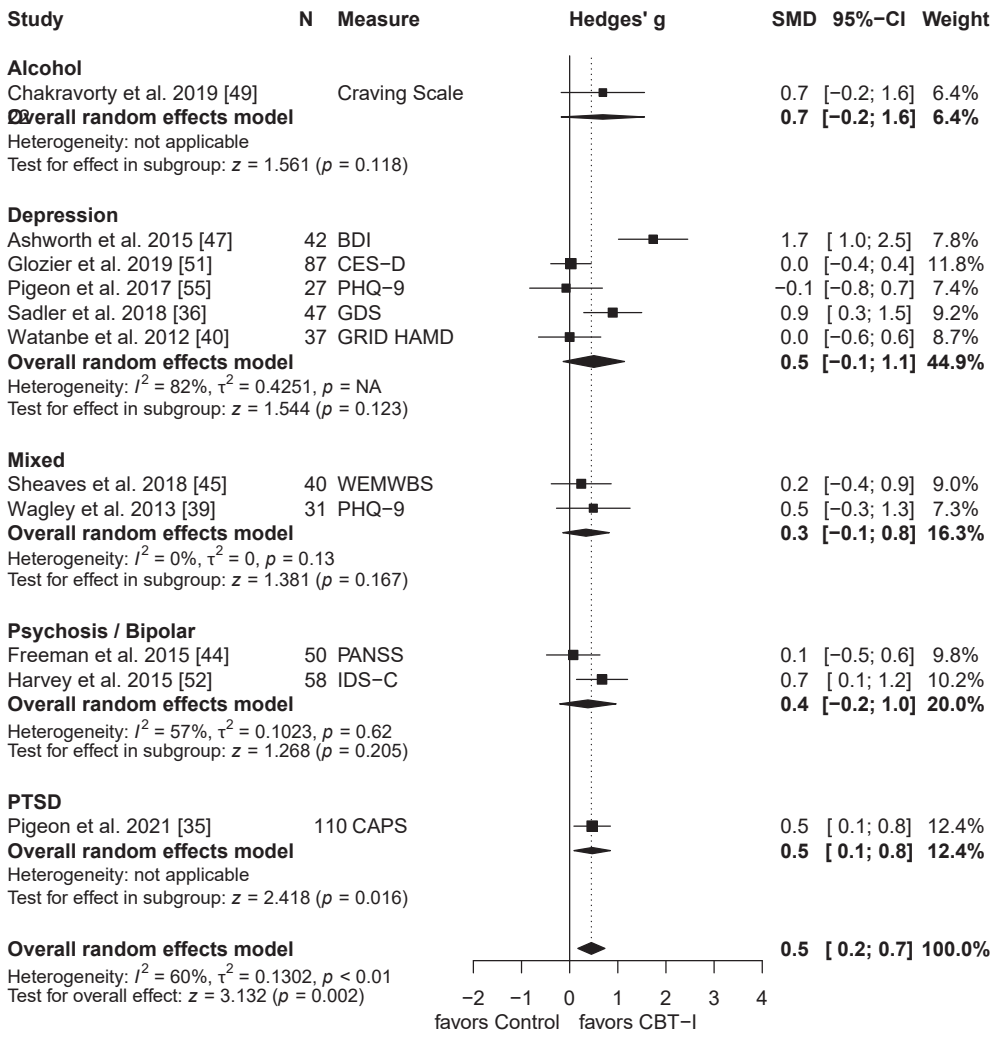

Fig. 5. Mental health at follow-up. BDI, Beck Depression Inventory; CES-D, Centre for Epidemiological Studies Depression Scale; GRID HAMD, Grid Hamilton Rating Scale for Depression; HAMD, Hamilton Rating Scale for Depression; IDS-C, Inventory of Depressive Symptomatology; PANSS, Positive and Negative Syndrome Scale; PHQ, Patient Health Questionnaire; WEMWBS, Warwick–Edinburgh Mental Wellbeing Scale. N, sample size (total sample).

and therefore remained significant at follow-up, they failed to reach significance for mental health at follow-up for subgroups (but did reach significance for the total sample of all studies). It remains unclear whether this points to a truly differential course of effect or rather reflects a statistical phenomenon.

The results of our meta-analysis are in line with current guidelines recommending CBT-I as the first-line treatment for chronic insomnia in adults [59–62] and highlight the importance of an insomnia-specific treatment in patients with a comorbid mental disorder. Here, CBT-I in addition to psychotherapeutic or pharmacological state-of-the-art treatment of the mental disorder results in better, long-lasting effects for both insomnia and the course of the mental disorder. In this meta-analysis, the effect sizes for insomnia severity in patients with comorbidity were moderate to large and therefore comparable to those found in patients with primary insomnia [9]. In patients with comorbidity, CBT-I should be understood as an add-on to psychotherapeutic and/or pharmacological treatment, not as a stand-alone treatment or replacement of disorder-specific treatment. Our results are generally well in line with previous meta-analyses investigating CBT-I in patients with comorbid insomnia. A direct comparison with the meta-analysis by Wu et al. [17] is difficult because they chose a different set of outcomes (remission from insomnia vs. severity of insomnia). In general, we replicate their finding that CBT-I is effective for patients with comorbid depression, and extend their findings by demonstrating that it is also effective for patients with PTSD, alcohol dependency, mixed comorbidities and potentially bipolar disorder and psychosis. Our results are also well in line with the finding by Gee et al. [18] that CBT-I has the potential to exert effects beyond insomnia and improve depression. We extend the findings of the Gee et al. meta-analysis by demonstrating that CBT-I also has the potential to reduce the symptoms of alcohol dependency and PTSD, but not those of bipolar disorder and psychosis.

Several limitations of this meta-analysis are related to the quality of the primary studies. Most included trials had relatively short follow-up periods. The majority of studies provided only one follow-up assessment, mostly three to six months after the end of treatment. More studies covering longer follow-up periods would be desirable especially with the aim of investigating long-term effects of an improvement of insomnia on the course of the mental disorder and potential preventive effects. In addition, 16 out of 22 included primary studies had a sample size equal to or below

Study Name	Randomization Process	Deviations From Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Bias
Arnedt et al. 2011 [46]	☺	☺	☺	☺	☺	☺
Ashworth et al. 2015 [47]	😐	☺	☹	☺	☺	☹
Carney et al. 2017 [48]	☺	☺	☺	☺	☺	☺
Chakravorty et al. 2019 [49]	☺	☺	☺	😐	☺	😐
Currie et al. 2004 [38]	☺	☺	☺	😐	☺	😐
Edinger et al. 2009 [50]	☺	☺	😐	☺	☺	😐
Freeman et al. 2015 [44]	☺	☺	☺	😐	☺	😐
Glozier et al. 2019 [51]	☺	☺	☺	😐	☺	😐
Harvey et al. 2015 [52]	☺	☺	☺	☺	☺	☺
Manber et al. 2008 [53]	☺	☺	☹	😐	☺	☹
Manber et al. 2016 [54]	☺	☺	☺	☺	☺	☺
O. Margolies et al. 2012 [41]	😐	😐	☺	😐	☺	😐
Pigeon et al. 2017 [55]	☺	☺	☺	😐	☺	😐
Pigeon et al. 2019 [56]	☺	😐	☺	😐	☺	😐
Pigeon et al. 2021 [35]	☺	☺	☺	☺	☺	☺
Sadler et al. 2018 [36]	☺	😐	☺	😐	☺	😐
Sheaves et al. 2018 [45]	☺	😐	☺	😐	☺	😐
Talbot et al. 2014 [57]	☺	☺	☺	😐	😐	😐
Taylor et al. 2015 [58]	😐	😐	☺	😐	☺	😐
Ulmer et al. 2011 [42]	😐	😐	☺	☹	☺	☹
Wagley et al. 2013 [39]	😐	☹	☺	😐	☺	☹
Watanabe et al. 2011 [40]	☺	😐	☺	😐	☺	😐
Total ☺	**17**	**14**	**19**	**7**	**21**	**5**
Total 😐	**5**	**7**	**1**	**14**	**1**	**13**
Total ☹	**0**	**1**	**2**	**1**	**0**	**4**

Fig. 6. Risk of bias rating. Low risk (green), moderate risk (yellow) and high risk (red). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

50. In addition, the funnel plots and the Egger tests indicated potential publication bias. It is conceivable that other trials may have been conducted but never published due to insignificant results. More large-scale trials on CBT-I in patients with psychiatric comorbidity would be desirable since small samples may have contributed to an overestimation of effect sizes. Conclusions regarding effects on mental health may be biased because in three studies, a specific psychiatric measure was not reported in the primary study and a measure of quality of life was included instead. Furthermore, many of the included primary trials have been conducted in specialist research settings with selected patient samples and highly trained or experienced therapists and their results may not translate to routine clinical practice. A further limitation of our study is that risk of bias ratings for all but two studies were performed by only one rater, potentially causing biased results. It was surprising that only six out of 22 included primary studies reported on adverse effects of CBT-I. Future clinical trials should adhere to recent recommendations for adequate monitoring and reporting of adverse events [63]. In this meta-analysis, behavioral elements of CBT-I were mandatory whereas cognitive therapy and relaxation were not. Twenty out of 22 primary studies conducted a form of CBT-I including the components education, behavioral treatment (sleep restriction and/or stimulus control), relaxation and cognitive therapy. There were only two studies focusing on behavioral therapy without relaxation and without cognitive elements. Therefore, we conclude that our results reflect CBT-I rather than behavioral therapy, despite our inclusion criteria.

Several studies investigated adapted versions of CBT-I. All studies by Pigeon et al., investigating patients with PTSD and depression, used a condensed version of CBT-I with only four sessions but including all common elements [35,55,56]. One study in depression and one study in a mixed population used a brief version focusing on behavioral elements called brief behavioral treatment [4,5]. Apart from one study in patients with depression [1] that was insignificant, the effects of the studies using abbreviated treatment versions had similar effect sizes compared to those using longer treatment periods. This indicates that brief versions of CBT-I, including those using behavioral treatment elements only, are also effective in patients with insomnia and mental comorbidity. Future research needs to clarify whether, and in which patient groups, brief behavioral therapy is sufficiently effective.

Six other studies adapted CBT-I for a specific patient group. These modifications were the inclusion of educational elements about the relationship between sleep and alcohol consumption [6], adaptations for patients with schizophrenia such as establishing daytime activity and circadian rhythms [7], adaptations for patients with bipolar disorder such as “wind down and wake up routines” [8], adaptations for psychiatric inpatients including circadian entrainment and strategies to manage worry and voices [9], and combining CBT-I with imagery rehearsal therapy for nightmares in patients with PTSD [10,11]. All the named studies with adaptations had good effects. However, since no study tested the adapted version against a non-adapted version of CBT-I, we cannot judge whether these adaptations would have been necessary to achieve the effects we see. From a theoretical point of view, the authors of this article speculate that it may even be a problematic development to adapt the CBT-I protocol for each comorbid disorder because patients with the same psychiatric diagnosis are often inhomogeneous. For example, a patient with an agitated presentation of depression may need different protocol adaptations compared to a patient with reduced psychomotor drive. Therefore, further research is needed to investigate whether manualized adaptations for specific patient groups are more effective than transdiagnostic protocols with individual adaptations for each patient. Transdiagnostic modifications for certain treatment modalities, e.g., for inpatients or those who are dependent on caretakers also seem highly promising [16,45].

Almost half of our sample of primary studies consisted of patients with depression. This shows that the focus of research into

comorbid insomnia is still strongly depression-focused, whereas we are only beginning to appreciate the high prevalence of insomnia in patients with other mental disorders. In addition, insomnia is not only a predictor for de novo onset of depression, but also increases the risk for the onset of anxiety disorders and substance dependency [3]. With three primary studies each, our meta-analysis indicates that CBT-I is effective in those with PTSD and alcohol dependency. Only one RCT each fulfilling our inclusion criteria has been conducted with patients suffering from bipolar disorder and psychosis. Other mental disorders known for high comorbidity with sleep disorders such as dependencies of substances other than alcohol, somatoform disorders, personality disorders, attention deficit hyperactivity disorder and eating disorders are not represented. In addition, authors largely investigated outpatients or previously untreated patients with mild or relatively stable comorbid disorders. To our knowledge, a form of CBT-I for acute insomnia in severely ill inpatients has only been investigated by two research groups [16,45]. This indicates a heightened need for research into the efficacy of CBT-I for patients with insomnia and previously under-researched patient groups.

Together, quantitative evidence demonstrates that insomnia is a risk factor for the de novo onset of mental disorders [3] and, as shown in the present work, improvement of insomnia symptoms is associated with improved mental health. Several theoretical models have been suggested to explain this link between sleep and mental health. One of them is the neuroplasticity hypothesis of depression [64,65]. Following this hypothesis, synaptic plasticity is disrupted in patients with depression. Sleep and sleep deprivation modulate synaptic plasticity. The exact mechanisms of therapeutic sleep deprivation are not completely understood. It is conceivable, however, that sleep loss in the context of insomnia, better sleep after CBT-I, and therapeutic sleep deprivation during sleep restriction therapy modulate symptoms of depression through changes in neuroplasticity.

Neurobiological models follow from the assumption that patients with insomnia suffer from substantial alterations of sleep, mainly reduced total sleep time resulting in sleep deprivation. Insomnia, however, is characterized by only small objective sleep deficits [68]. Hallmarks of insomnia are subjective sleep disturbances and dysfunctional thoughts and attitudes about sleep. Daytime sleepiness as a characteristic effect of sleep deprivation is not present in patients with insomnia [69]. In principle, it is conceivable that not sleep deprivation, but rather stress and worry about sleep are responsible for adverse effects on mental health. Since chronic stress can lead to depression, stress induced by constant worry about sleep may play a role in the development of depression [70–73]. CBT-I also improves dysfunctional thoughts and attitudes about sleep [73]. Therefore, improved mental health after CBT-I may be attributable to reduced worry about sleep rather than improved sleep itself. Further research is needed to disentangle the potentially differential effects of objective sleep loss and psychological symptoms of insomnia on mental health in future interventional studies.

In conclusion, CBT-I is highly effective for patients with mental disorders and comorbid insomnia. Further dissemination of CBT-I in this patient group is a priority for clinical sleep research. A future research agenda should focus on 1) investigating the efficacy of CBT-I for patients with insomnia and under-researched comorbidities such as psychosis, bipolar disorder, ADHD, eating disorders, personality disorders and somatoform disorders, 2) investigate the potential of CBT-I for the prevention of the de novo onset of mental disorders and/or the prevention of new episodes of mental disorders in those who were already diagnosed, and 3) investigate the efficacy of disorder-specific adaptations of certain mental disorders versus transdiagnostic approaches.

Practice points

1) Cognitive Behavioral Therapy for Insomnia (CBT-I) is effective in patients with mental disorders and comorbid insomnia.
2) CBT-I reduces insomnia severity (large effect size) and the severity of the comorbid disorder (medium effect size).
3) Depression, post-traumatic stress disorder and alcohol dependency are the comorbid disorders with the best evidence base for CBT-I.

Research agenda

Novel prospective research should include trials investigating the efficacy of CBT-I for patients with previously under-investigated comorbidities, the efficacy of adaptations of the CBT-I protocol compared to the standard protocol, follow-up periods longer than 6 mo, and the potential of CBT-I for the prevention of mental disorders.

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Conflicts of interest

The authors do not have any conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101597.

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