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CLINICAL REVIEW

Psychosocial intervention for discontinuing benzodiazepine hypnotics in patients with chronic insomnia: A systematic review and meta-analysis

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SUMMARY

Long-term benzodiazepine (BZD) use is not recommended in the treatment of chronic insomnia, and psychosocial interventions, particularly cognitive behavioral therapy for insomnia (CBT-I), are a potential treatment option for discontinuing BZDs. This systematic review and meta-analysis aimed to clarify whether psychosocial interventions are effective for discontinuing BZD hypnotics in patients with chronic insomnia.

A literature search of major electronic databases was conducted up to July 2018. Two researchers independently selected relevant publications, extracted data, and evaluated methodological quality according to the Cochrane criteria.

Eight randomized-controlled trials, all of which evaluated CBT-I, were included in this review, and meta-analyses were performed. The results indicated that short-term (≤3 mo) CBT-I plus gradual tapering was more effective than gradual tapering alone for discontinuing BZDs hypnotics (risk ratio: 1.68, 95% confidence interval [CI]: 1.19−2.39, p = 0.003) and for improving insomnia symptoms (g: −0.69, 95% CI: −1.09 − −0.28, p = 0.0009). However, the long-term (12 mo) efficacy of CBT-I for discontinuing BZDs was not significant (risk ratio: 1.67, 95% CI: 0.91−3.07, p = 0.10). Thus, CBT-I is effective for discontinuing BZD hypnotics for ≤3 mo. Further studies are needed to clarify the long-term efficacy of psychosocial interventions for discontinuing BZD hypnotics.

Introduction

Insomnia is a common disorder with a prevalence of 15%−24% [1−3]. Chronic insomnia is known to be associated with subjective daytime fatigue, low energy, difficulties in cognitive performance, and deteriorated quality of life [4]. Benzodiazepines (BZDs) and BZD receptor agonists have long been recognized as the mainstay of

Abbreviations: BZDs, Benzodiazepines; CBT-I, cognitive behavioral therapy for insomnia; CI, confidence interval; RCTs, randomized controlled trials.

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treatment options for chronic insomnia. However, the disadvantages of the long-term use of BZD hypnotics such as cognitive function decline [5], risk of falls [6], and development of tolerance and dependence [7,8], have been reported [9–11]. Therefore, the clinical guidelines of the American Academy of Sleep Medicine suggest that long-term hypnotic treatment can be indicated only for patients with severe or refractory insomnia or chronic illness [12]. It is also suggested that BZDs should only be used for a short-term period of up to 4 wk to prevent the occurrence of the disadvantages associated with long-term use [13]. Despite caution concerning the risks associated with long-term BZD use, BZD hypnotics are commonly prescribed to patients with chronic insomnia worldwide [14].

Discontinuing the long-term use of BZD hypnotics in patients with chronic insomnia is an important issue in the reduction of the risk of these adverse effects. However, abrupt discontinuation of these medications is likely to cause withdrawal symptoms including rebound insomnia [15]. Although some strategies for discontinuing BZD hypnotics, including gradual tapering, pharmacological interventions, and psychosocial interventions, have been proposed, the most effective approach is unclear [16–20].

Psychosocial interventions are recommended in the clinical guidelines [12]. Cognitive behavioral therapy for insomnia (CBT-I) is an effective psychosocial intervention, which typically includes relaxation training, stimulus control, sleep restriction, and cognitive therapy. Several guidelines recommend CBT-I as the first-line treatment for patients with chronic insomnia [12,13,21] due to its efficacy for improving insomnia and the minimal adverse effects, compared to pharmacological treatment [22]. Previous randomized controlled trials (RCTs) have suggested that CBT-I plus gradual tapering of BZDs was more effective than gradual tapering of BZDs alone for discontinuing BZD hypnotics as well as improving the severity of insomnia [23,24]. However, other RCTs have reported no significant differences between CBT-I and gradual tapering with regard to the discontinuation of BZD hypnotics [25,26]. Therefore, the efficacy of CBT-I for discontinuing BZD hypnotics remains unclear. In addition, recent studies have suggested that other psychosocial interventions, such as aerobic exercise [27–29] and mindfulness-based therapy [30,31], were also effective for the treatment of chronic insomnia, and may be considered as potential alternative therapies for discontinuing BZD hypnotics.

Thus, we aimed to conduct a systematic review and meta-analysis to clarify whether psychosocial interventions, including CBT-I, are effective for discontinuing BZD hypnotics in patients with chronic insomnia. We also aimed to investigate the advantages of psychosocial interventions for discontinuing BZD hypnotics as well as improving the severity of insomnia compared to simple gradual tapering of BZDs in the short- and long-term.

Methods

This study was conducted in accordance with the PRISMA recommendation for reporting systematic reviews and meta-analyses [32] and preregistered with PROSPERO [33], registration #: CRD42018115649.

Search strategy

We searched the electronic databases of PubMed (search date: July 4, 2018), Cochrane Central Register of Controlled Trials (CENTRAL; search date: Oct 31, 2018), and Embase (search date: Oct 10, 2018) for reports of RCTs using appropriate subject headings and search syntaxes, which were relevant to each resource (e.g., insomnia, cognitive behavioral therapy, and tapering; Table S1).

Inclusion criteria

Publications meeting the following criteria were included in the final review:

1) At least 80% of the participants diagnosed with chronic insomnia according to study diagnoses (diagnosed using any recognized diagnostic criteria)
2) More than 80% of the participants taking BZD hypnotics
3) Interventions comprised cognitive and/or behavioral treatment strategies aimed at treating insomnia containing any combination of stimulus control therapy, sleep restriction therapy, relaxation therapy, and/or psychoeducation plus gradual tapering of BZDs
4) Participants randomized to minimal intervention, such as sleep hygiene education, plus gradual tapering of BZD hypnotics as a control condition
5) Pre- and post-treatment data provided for both intervention and control groups for information regarding dosage and/or number of hypnotics.
6) RCTs

Article selection process

Two authors (IO and AS) independently eliminated duplicates. Subsequently, two groups to which two authors belonged were created (AS and AI, and MS and TU). In each group, the two authors independently screened the titles and abstracts of the identified references with the purpose of excluding irrelevant studies. Four groups in which two authors belonged were then created (KK and IO, IO and AS, HY and NK, and MS and TU). The full texts of these references were evaluated and ineligible reports were excluded according to the above criteria and the reasons for exclusion were registered by the authors in each group. Any disagreement was resolved by systematic and thorough discussion with another author (YT).

Outcome measures

Outcome measures included rate of hypnotic discontinuation after the intervention and 12 mo after the intervention and improvement in insomnia severity after the intervention and 12 mo after the intervention. We also included outcomes of the rate of any adverse events, a 50% reduction in the use of hypnotics, and daytime dysfunction.

Study quality and risk of bias assessment

Three groups to which two authors belonged were made (IO and AS, HY and NK, and MS and TU). The authors in each group independently extracted the data and another author (YT) performed checks to ensure accuracy. The following variables were recorded: participant characteristics, diagnostic criteria of insomnia, study design, details of the treatment component, treatment duration, control intervention, and outcome measures. The quality of the included studies was evaluated by two authors (IO and AS, HY and NK, and MS and TU) in each group using the Cochrane risk of bias assessment [34]. The assessment evaluates RCTs in seven domains, including random-sequence generation; allocation concealment; blinding of participants; personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The ratings of each domain can be “yes” (low risk of bias), “no” (high risk of bias), or “unclear” (uncertain risk).

Disagreements were resolved by systematic and thorough discussion with YT.

Statistical analyses

We used the Cochrane Collaboration Review Manager software (RevMan 5.3) for statistical analysis. Continuous outcome data were summarized using effect size, with 'standardized mean differences', with 95% confidence intervals (CIs); for dichotomous outcomes, risk ratios with 95% CIs were used. We used random effects models in the data analyses. Publication bias was evaluated by a funnel plot of treatment effect against standard error and Egger's test when at least 10 studies were available [34]. Assessments of treatment adherence, acceptability, perceived utility, and credibility were reviewed. Subgroup analysis was performed by psychiatric comorbidity (chronic insomnia with vs without psychiatric comorbidity) to investigate the source of heterogeneity.

Results

Description of studies included for review

The initial literature search yielded 3349 results after exclusion of duplicates (PubMed = 2,567, Embase = 2,038, CENTRAL = 260) and additional records were identified through other sources (n = 7) up to July 2018. After reading the titles and abstracts of the identified reports, the full-texts of 163 articles were retrieved, with 151 being excluded due to various reasons (Table S2). The remaining 12 RCTs were included in a qualitative synthesis, and eight of these RCTs were included in a quantitative synthesis (Fig. 1).

Study characteristics

A total of eight studies published between 1983 and 2018 were included in this review [23–26,35–42]. The sample size of the eight studies included in the meta-analysis ranged from 20 to 209, with a total of 482 participants (Table 1). Approximately 61.3% of the sample was female and the participants' mean age was 60.7 y. The criteria used for the diagnosis of insomnia varied across studies. Four studies used the diagnostic and statistical manual of mental disorders, fourth edition; two studies used the international classification of sleep disorders; and three studies did not describe the details of the diagnostic criteria for insomnia. Polysomnography screening was performed in two studies. To exclude psychiatric comorbidity, structured or semi-structured interviews for psychiatric disorders were performed in two studies [24,37,40]. Three studies excluded psychiatric comorbid insomnia based on clinical interviews or self-reports [25,26,35,39]. The three remaining studies included psychiatric comorbidities [23,36,38,41,42]. All subjects included in the eight RCTs consumed hypnotics. Only one study permitted participants to use antidepressants [38]. The other studies prohibited the use of any concomitant medications that may have affected insomnia symptoms.

Of the eight studies, seven were individual RCTs [24–26,35–38] and one was a cluster RCT [23,42]. There were six two-arm studies [25,35] and two three-arm studies [23,24,26,36–38,42]. As the three-arm studies involved two separate comparisons, the total number of comparisons was greater than the number of studies included in this review. When a three-arm study consisted of two different interventions, we selected only one intervention, which was consistent with gradual tapering.

Treatment components of the CBT-I programs varied across the studies (Table 2). Across the eight studies, five provided a multicomponent CBT-I program consisting of at least one behavioral, one cognitive, and one educational component [23–25,35,37,42]. Self-help CBT with booklets comprised weekly: 1) information regarding insomnia; 2) instructions for stimulus control and sleep restriction procedures; 3) information regarding cognitive therapy; 4) sleep hygiene education; and 5) guidance for evaluating progress and examining possible reasons for lack of improvement, and strategies for relapse prevention, was used in one study [26]. One study used group CBT-I treatment with an eight weekly group session of 90 min duration. One month after the final session, the

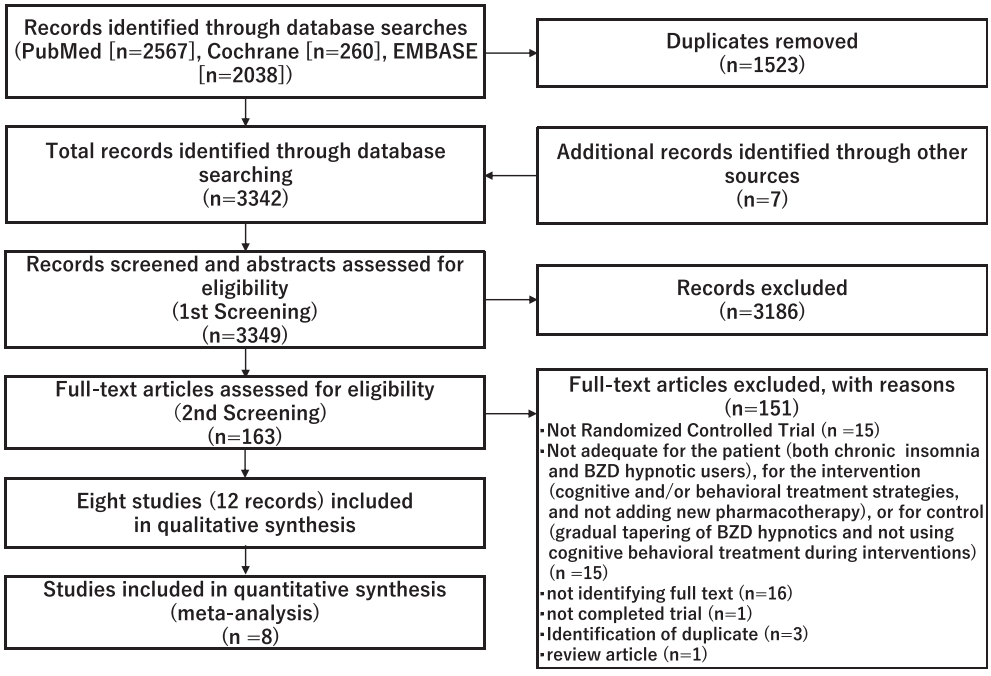

Fig. 1. Flowchart of the study selection process for the studies included in the review.

Table 1
Sleep health outcome.

Study (year)	Enrolled Patients[a]	Study Design	Diagnostic criteria for chronic insomnia	Sleep health Outcome	Sleep health outcomes at post intervention[b]	Sleep health outcomes at long-term follow-up[b]	Rate of discontinuation of BZD	Assessment of discontinuation of BZD	Country	Attrition[c]
Baillargeon et al. (2003) [35]	65 adults (mean age = 67.4 y)	RCT two-arm	Insomnia for a period of 6 mo or more (ICSD [1990])	• BZDs-free • Dosage reduction of ≥50%	At 0 wk: ↓BZD-free (CI 1.8−16.2) ↓Dosage reduction of ≥50% (CI 2.5−284.3)	At 12 mo: ↓BZD-free (CI 2.4 −23.7) ↓Dosage reduction of ≥50% (CI 1.3−13.6)	CBTI:26/ 34 = 0.76 control:11/ 29 = 0.38	Based on self-reported sleep diary and confirmed by blood screening	Canada	62/65 = 95.4%
Ayabe et al.(2018) [25]	51 adults (mean age = 59.8 y)	RCT two-arm	Persistent primary insomnia (DSM-IV-TR) despite undergoing pharmacotherapy with hypnotics for 3 mo	• ISI • SDS • Hypnotic (diazepam) dose equivalent	At 2 wk: ↓ISI ($p < 0.05$) ↓SDS (42.00 ± 2.15 vs 41.49 ± 1.82)[d] ↓Hypnotic dose (7.41 ± 1.78 vs 7.52 ± 1.65)	Long-term follow up data not collected	CBTI:0/23 = 0 control:2/ 26 = 0.08	Based on self-reported sleep diary	Japan	49/51 = 96.1%
Giblin et al.(1983) [36]	20 adults (mean age = 71.3 y)	RCT two-arm	Using hypnotics nightly for ≥6 mo (Research diagnostic criteria);	• The amount of hypnotic usage	At 1 mo: ↓hypnotic usage but no statistical analysis	Long-term follow up data not collected	CBTI:7/10 = 0.7 control:1/ 10 = 0.1	Based on self-report	England	10/10 = 100%
Lichstein et al.[d](2003) [37]	47 adults (mean age = 63.5 y)[c]	RCT three-arm	Difficulty initiating or maintaining sleep lasting ≥6 mo (DSM-IV, ICSD-revised)	• GDS • Drug-free • Medication consumption means	At 0 wk: ↓GDS (6.0 ± 5.0 vs 5.2 ± 4.9) ↑drug-free but ns ↓medication consumption (0.2 ± 0.6 vs 0.3 ± 0.7)	At 1 y: ↓GDS (4.6 ± 3.2 vs 6.4 ± 4.5) ↑drug-free but ns ↓medication consumption (0.3 ± 0.6 vs 0.7 ± 1.4	CBTI:16/ 22 = 0.73 control:12/ 19 = 0.63	Based on self-reported sleep questionnaire	America	40/47 = 85%
Wang et al.(2016) [38]	79 adults (mean age = 41.2 y)	RCT two-arm	Sleep complaint lasting ≥1 mo (Sleep Disorder Research Group of the Neurology Chapter of Chinese Medical Association), hypnotic use for ≥6 mo (administered continuously for ≥4 wk)	• ISI • ESS • Stopping using BZDs • Average nightly dose of BZDs	At 4 wk: ↓ISI (7.96 ± 1.99 vs 11.36 ± 2.52) ↓ESS (2.36 ± 2.60 vs 5.03 ± 3.44) ↑stopping using BZDs ($p < 0.05$) ↓Dose of BZDs ($p < 0.01$)	Long-term follow up data not collected	CBTI:8/ 30 = 0.27 control:2/ 29 = 0.07	N/S	China	79/79 = 100%
Morgan et al.(2004) [23,41,42]	209 adults (mean age = 65.43 y)	Cluster-RCT two-arm	A persistent (≥1 month) complaint of difficulty initiating or maintaining sleep (DSM-IV/ICD-10)	• PSQI • SF-36 (MH) • Zero hypnotic use • Mean hypnotic dose	At 3 mo: ↓PSQI ($p = 0.002$) ↑SF-36 (MH) ($p = 0.14$) ↑zero hypnotic use ($p = 0.005$) ↓hypnotic dose ($p = 0.21$)	At 12 mo: ↓PSQI ($p = 0.01$) ↑zero hypnotic use (0.008) ↑hypnotic dose ($p = 0.57$)	CBTI:22/ 76 = 0.29 control:8/ 75 = 0.11	Based on self-reported drug log	England	103/209 = 49.3%
Belleville et al.(2007) [26,39]	53 adults (mean age = 55.3 y)	RCT two-arm	Use of a medication to promote sleep [BZD, zopiclone, or zaleplon] >3 nights per wk for ≥3 mo, and difficulty with initiating or maintaining sleep >3 nights per wk for ≥6 mo (original criteria)	• ISI • BDI • Drug-free participants among available sample • Daily quantity of hypnotic medication used (lorazepam equivalent in mg)	At 0 wk: ↓ISI (11.73 ± 5.14 vs 14.25 ± 6.05) ↓BDI (7.32 ± 6.31 vs 4.21 ± 3.67) ↑Drug-free participants among available sample (16 [72.7%] vs 16 [64.0%]) ↓Daily quantity of hypnotic medication used (0.17 ± 0.40 vs 0.09 ± 0.20)	Long-term follow up data not collected	CBTI:16/ 22 = 0.73 control:16/ 25 = 0.64	Based on self-reported sleep diary	Canada	48/53 = 90.6%

Morin et al.[e](2004) [24,40]	52 adults (mean age = 63.0 y)	RCT 3-arms	Difficulties initiating and/or maintaining sleep >3 nights per wk and ≥6 mo (ICSD (1990))	• ISI • Drug-free subjects • Weekly quantity of BDZs used (diazepam equivalent in mg)	At 0 wk: ↓ISI (11.18 ± 1.06 vs 12.72 ± 1.12) ↑Drug-free (23 [85%] vs 12 [48%]) ↓Weekly quantity of BDZs (1.30 ± 6.34 vs 11.40 ± 6.72)	At 12 mo: ↓ISI (11.06 ± 1.11 vs 9.97 ± 1.18) ↑Drug-free (16 [59%] vs 13 [52%]) ↓Weekly quantity of BDZs (4.43 ± 6.62 vs 13.28 ± 7.09)	CBTI:23/27 = 0.85 control:12/25 = 0.48	Based on self-reported sleep diary and confirmed by estimations in plasma and urine	Canada	47/52 = 90.4%

BDI = Beck depression inventory, BZDs = benzodiazepines, CI = confidence interval, DSM = diagnostic and statistical manual of mental disorders, ESS = Epworth sleepiness scale.
GDS = geriatric depression scale, ICSD = international classification of sleep disorders, ISI = insomnia severity index, ns = non-significant, PSQI = Pittsburgh sleep quality index.
RCT = randomized controlled trial, SDS = self-rating depression scale, SF-36(MH) = the 36-Item short form health survey (mental health).

[a] Number of patients meeting inclusion criteria, enrolled into the study at baseline.

[b] Arrows indicate the effect on the difference of the post intervention and baseline. Values in parentheses indicate statistical analysis results of variables before and after intervention, and are indicated in the following order: a; p value, b; 95% CI (odds ratio), c; mean ± standard deviation or standard error (intervention vs control), d; Number (%) (intervention vs control).

[c] Attrition is calculated as a proportion of participants (both intervention and control) at the final follow-up point, relative to the number of participants randomized at baseline.

[d] Focusing on multi-component cognitive behavioral therapy group and scheduled withdrawal group.

[e] Focusing on patients receiving medication tapering, and patients receiving combined cognitive behavioral therapy and medication tapering.

participants were invited to a "booster" session to reinforce the skills acquired during group therapy [35]. Another study used classic CBT-I treatment, which involved a 4 wk manual-based intervention that included two in-person sessions on wk one and three, and two telephone "booster" sessions on wk two and four conducted by a clinical psychologist [38]. One study used original psychotherapy, which included relaxation and psychoeducation [36].

Risk of bias assessment

From the risk of bias summary (Fig. 2), five RCTs reported an adequate randomization method [24–26,35,38] and three RCTs reported a sufficient allocation concealment procedure [25,26,38]. All RCTs were judged to have a high risk of bias with regard to participant and personnel blinding because of the nature of these studies. In terms of attrition bias, seven studies provided adequate statistical handling of missing data [24–26,35–38], while one study was deemed to carry a high risk of attrition bias due to the absence of statistical handling for missing data [23,42]. Reporting bias was unclear in seven studies because we were unable to obtain the research registration of these studies [23,24,26,35–38]. There was potential unit-of-analysis bias in one study due to the cluster RCT design [23,42].

Treatment outcome assessment

The rate of discontinuation of BZD hypnotics after the intervention was the main primary outcome measure reported across all eight RCTs [23–26,35–38]. Seven RCTs also assessed the number of participants who achieved a 50% reduction in the use of BZDs hypnotics between baseline and after the intervention [23–26,35–38]. Subjective sleep questionnaires (insomnia severity index = 4, Pittsburgh sleep quality index = 1) were reported in five studies [23–26,38]. Four studies reported adverse events relevant to the interventions [24–26,35]. Five studies evaluated daytime dysfunction including depressive symptoms, anxiety symptoms, and mental health-related quality of life scales (Self-rating Depression Scale = 1, Beck depression inventory = 1, geriatric depression scale = 1, 36-item short form health survey = 1, Epworth sleepiness scale = 1) [23,25,26,37,38]. Concerning long-term outcomes, two studies assessed the severity of insomnia symptoms 12 mo after the intervention [23,24] and four studies evaluated the rate of discontinuation of BZD hypnotics 12 mo after the intervention [23,24,35,37].

Post-intervention assessments were carried out immediately after the intervention (two studies) and at 2 wk (one study), 4 wk (one study), and 3 mo (one study) after the intervention. With respect to the control group included in the meta-analysis, 64 out of a total of 238 participants (26.9%) successfully discontinued BZD hypnotics post-intervention. If we assume that insomnia patients not receiving CBT in our own practice achieved this outcome at the same proportion, the discontinuation rate of BZD hypnotics in the CBT-I group post-treatment would be estimated as 45.2% (95% CI: 32.0%–64.3%), using the pooled Relative Risks calculated in the meta-analysis (1.68, 95% CI: 1.19–2.39, p = 0.003; 482 participants, eight studies) (Fig. 3). The scores of subjective sleep questionnaires were significantly improved in the CBT-I group compared to the control group (g: −0.69, 95% CI: −1.09 − −0.28, p = 0.0009; 372 participants, five studies) (Fig. 4). However, no significant differences in daytime dysfunction (g = −0.09, 95% CI: −0.55 − 0.37, p = 0.70; 360 participants, five studies) (Fig. 5) or a 50% reduction in the rate of BZD hypnotics use (risk ratio: 1.27, 95% CI: 0.94–1.70, p = 0.11; 352 participants, seven studies) were found between the two groups (Fig. 6). Regarding long-term outcomes (12 mo after the

Table 2
Description of cognitive behavioral therapy for insomnia interventions.

Study (year)	Setting: primary or secondary care	Referral	Provider of intervention (CBT)	CBT-I training provided	Treatment (intervention) vs control	Gradual tapering method	Treatment fidelity	Format	Number, duration, and time frame of sessions
Baillargeon et al.(2003) [35]	Secondary care	Family physicians + media advertisements	Specially trained psychologist	Special training for CBT (Charles M. Morin)	(SCT, SRT, CT, SHE, gradual tapering) vs gradual tapering	Began with the CBT-I, supervised by a physician (met weekly over an 8-wk period), 25% reduction of dosage at 1-or 2-wk intervals depending on the patient's symptoms.	All of sessions were audiotaped and reviewed regularly with the project director to optimize adherence to the treatment protocol.	Group (5−7 participants)	8 + booster sessions (1 mo after the last session), 90 min, and 8 wk
Ayabe et al.(2018) [25]	Secondary care	Outpatient sleep specialist physician	Clinical psychologists	Providers had been trained with the same treatment manual	(PE [SHE included], RL, SCT, SRT, gradual tapering) vs TAU [general sleep hygiene leaflet], gradual tapering	Tapering started from Session 4, with the quantity (mg) of the diazepam dose equivalent reduced by 1/4. During the 4 wk post intervention period, patients were permitted to taper the drug dose by another 1/4.	The same multicomponent approach (training via the same treatment manual) to ensure treatment consistency across all facilities	Individual	5, 50 min, and 10 wk
Giblin et al.(1983) [36]	N/A	Letter + interview (by GP)	Clinical psychologist	N/A	(Autogenic relaxation, information about sleep, general advice, tapering) vs tapering	Asked to stop taking hypnotics, and to refrain from using hypnotics for as long as patients could.	N/A	Individual	4, 60 min, and 4 wk
Lichstein et al.[a](2003) [37]	Secondary care	Media announcements	Graduate students in clinical psychology served as therapists	Guidance from treatment manuals	(RL, SCT, SHE, gradual-withdrawal) vs gradual-withdrawal	1st step (>1 LRD, in the first wk, hypnotics were cut by 1/4 of the dosage on half of the HD nights, which continued until tapered to one LRD. 2nd step (non HD night): 0.5 LRD was eliminated on two nonconsecutive nights.	Induction strategies; assessment to determine the degree of implementation for each treatment; providers were monitored by audiotape to assess accurate performance.	Individual	8, 45 min, and 8 wk
Wang et al.(2016) [38]	Secondary care	Recruitment from university hospital outpatients (psychology department)	Two clinical psychologists	N/A	(SHE, SRT, SCT [two in-person sessions on wk one and 3], telephone follow-up [wk two and 4], gradual taper) vs SHE, gradual taper	If the patients reported improved sleep, a 25% reduction of the initial BZD dose per wk was considered.	Manual-based intervention; Session 2 was used as a brief "check-in" to provide support and to problem-solve issues regarding treatment adherence. Session 3 was used to monitor and reinforce adherence to treatment recommendations.	Individual	4, ~60 min (wk 1) ~15 min (wk 2, 4) ~30 min (wk 3), and 4wk
Morgan et al.(2004) [23,41,42]	Primary care	GP + letter	Two experienced primary care counsellors	40 h of classroom-based training in psychological (cognitive −behavioral) approaches to insomnia management	(SHE, SRT, SCT, RT, CT) vs no additional treatment	If patients expressed an interest in reducing drug dosage, low frequency drug use (≤50% of the baseline drug-use frequency) was encouraged (started tapered program)	Fortnightly clinical supervision (by a consultant clinical psychologist experienced in the cognitive-behavioral treatment of chronic insomnia) to maintain the quality of treatment and to provide clinical support for the counsellors.	Individual	6, 50 min, and 6 wk
Belleville et al.(2007) [26,39]	Secondary care	Media advertisement	Two clinical psychology graduate students (weekly phone call)	Supervised by a clinical psychologist experienced in insomnia treatment (Charles M. Morin).	(Self-help CBT with five booklets provided weekly [SCT, SRT, CT, SHE], tapering) vs tapering	1) setting goals, 2) stabilization with the use of a single hypnotic, 3) dosage reduction by about 25% every 2 wk, 4) drug-free nights were introduced, 5) nights with and without hypnotics were planned	Follow the CBT guidelines; a composite score of adherence to CBT recommendations, audio recorded sessions (20% were reviewed for treatment integrity).	Individual	5, N/A (due to handbook), and 8 wk

Morin et al.[b](2004) [24,40]	Secondary care	Newspaper advertisements + physicians' referrals	A master's-level clinical psychologist	Treating a minimum of four patients by using this treatment (before participating in this study)	(SRT, SCT, CT, SHE, tapering) vs tapering	1) setting goals, 2) stabilization with the use of a single BZD, 3) dosage reduction by about 25% every 2 wk, 4) introduction of an increasing number of drug-free nights, 5) scheduled hypnotic use rather than use on an as-needed basis.	All sessions recorded and reviewed regularly with the project director to optimize adherence to the treatment protocol.	Group (four to six patients)	10, 90 min, and 10 wk

CBT-I, cognitive behavioral therapy for insomnia, CT = cognitive therapy, GP = general practitioner, PE = psychoeducation, RL = relaxation therapy, SCT = stimulus control therapy, SHE = sleep hygiene education, SRT = sleep restriction therapy, TAU = treatment as usual, LRD = lowest recommended dosage, HD = high dose.

[a] Focusing on multi-component cognitive behavioral therapy group and scheduled withdrawal group.

[b] Focusing on patients receiving medication tapering, and patients receiving combined cognitive behavioral therapy and medication tapering.

intervention), no significant differences were observed in the rate of BZD hypnotic discontinuation (risk ratio: 1.67, 95% CI: 0.91–3.07, p = 0.10; 256 participants, four studies) (Fig. 7) or improvement in subjective sleep questionnaire scores (g = −0.19, 95% CI: −0.88–0.49, p = 0.58; 155 participants, two studies) (Fig. 8) between the two groups.

Results of subgroup analyses showed that there were no significant differences between participants with chronic insomnia, with and without psychiatric comorbidity, with regard to subjective insomnia scores; daytime dysfunction; rate of discontinuing BZDs; or 50% reduction in the rate of BZD use, post-intervention (Figs. 3–6). However, there were significant differences in the rate of discontinuing BZDs (risk ratio: 3.33, 95% CI: 1.22–9.07, p = 0.02 vs risk ratio: 1.43, 95% CI: 0.77–2.64, p = 0.25) and subjective insomnia scores (g = −0.52, 95% CI: −0.92 – −0.12, p = 0.01 vs g = 0.18, 95% CI: −0.36–0.73, p = 0.51) at 12 mo after the intervention (Figs. 7 and 8).

Discussion

This is the first systematic review and meta-analysis to evaluate the efficacy of CBT-I in discontinuing BZD hypnotics. The results of this review suggest that CBT-I is effective for the short-term (≤3 mo) discontinuation of BZD hypnotics as well as

Fig. 2. Risk of bias assessment summary.

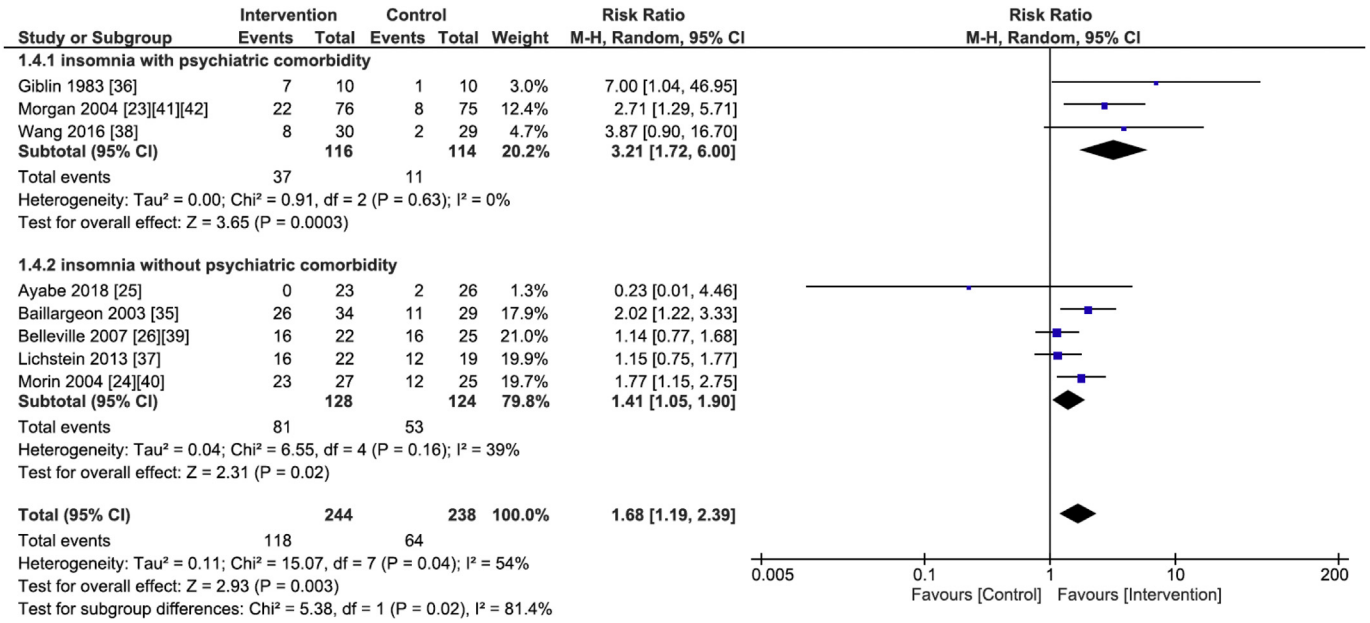

Fig. 3. Forest plot of treatment effect sizes for post-intervention rate of benzodiazepine hypnotic discontinuation. CI, confidence interval.

improvement of insomnia symptoms. However, the effects of CBT-I for discontinuing long-term (12 mo) BZD use did not reach statistical significance ($p = 0.10$). Although the reason for this phenomenon is unclear, it is possible that the accuracy and power of detecting significant differences in the long-term efficacy of CBT-I for discontinuing BZD hypnotics was insufficient due to the small sample sizes employed.

Previous studies have suggested that there were no significant effects of alternative pharmacological treatment, particularly melatonin, in discontinuing BZD hypnotics [20]. Consequently, we conducted this systematic review and meta-analysis focusing on psychosocial interventions. As a result, eight studies were included in our review, all of which evaluated CBT-I or related psychological interventions. Some studies included in this review reported that CBT-I plus gradual tapering was more effective in discontinuing BZD hypnotics than was gradual tapering in the short-term period [23,24,35,36,42], but other studies did not report a significant effect of discontinuing BZDs using CBT-I plus tapering [25,26,37,38]. The result of our meta-analysis revealed that CBT-I plus tapering was significantly more effective in discontinuing BZDs in the short-term period. In addition, our results also suggested that CBT-I was effective for improving insomnia symptoms in the short-term period as observed in previous systematic reviews and meta-analyses [43,44]. Therefore, CBT-I can be recommended for discontinuing BZDs, which was supported by robust evidence, at least for a short-term period.

In contrast, few RCTs have evaluated the long-term effects of CBT-I for insomnia symptoms [45–48], and systematic reviews analyzing pooled data from these studies, including our review, have not reported a significant effect [43]. Typically, chronic insomnia is likely to persist, with the clinical course being characterized by repeating periods of remission and relapse. A recent study has suggested that some residual symptoms can affect relapse of insomnia after achieving a remission in the long-term

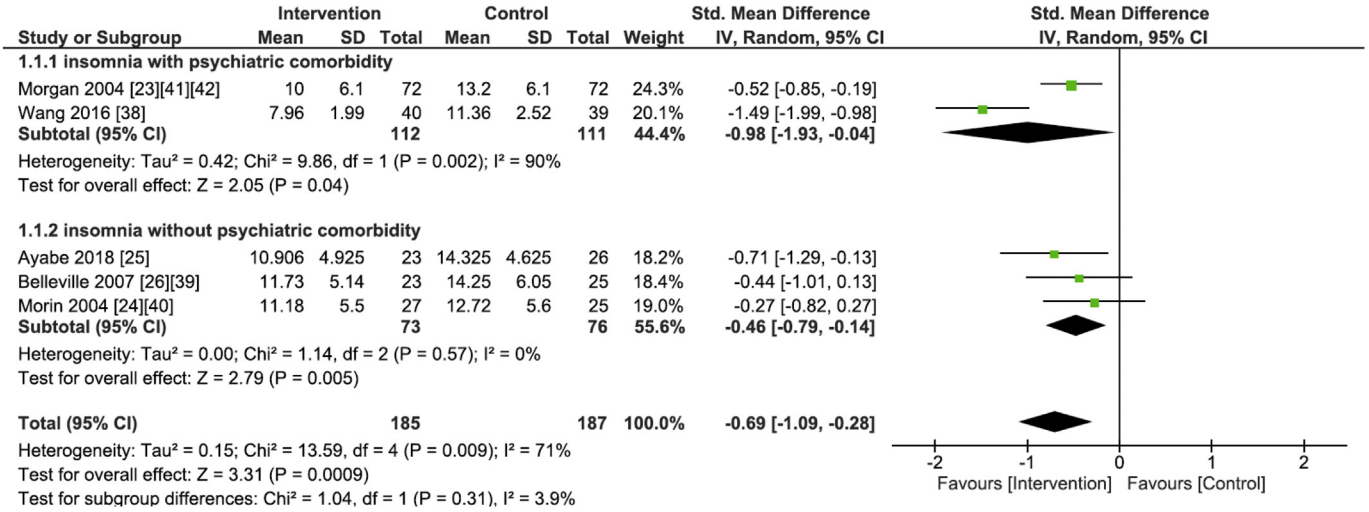

Fig. 4. Forest plot of treatment effect sizes for post-intervention improvement in subjective insomnia severity. CI, confidence interval; SD, standard deviation.

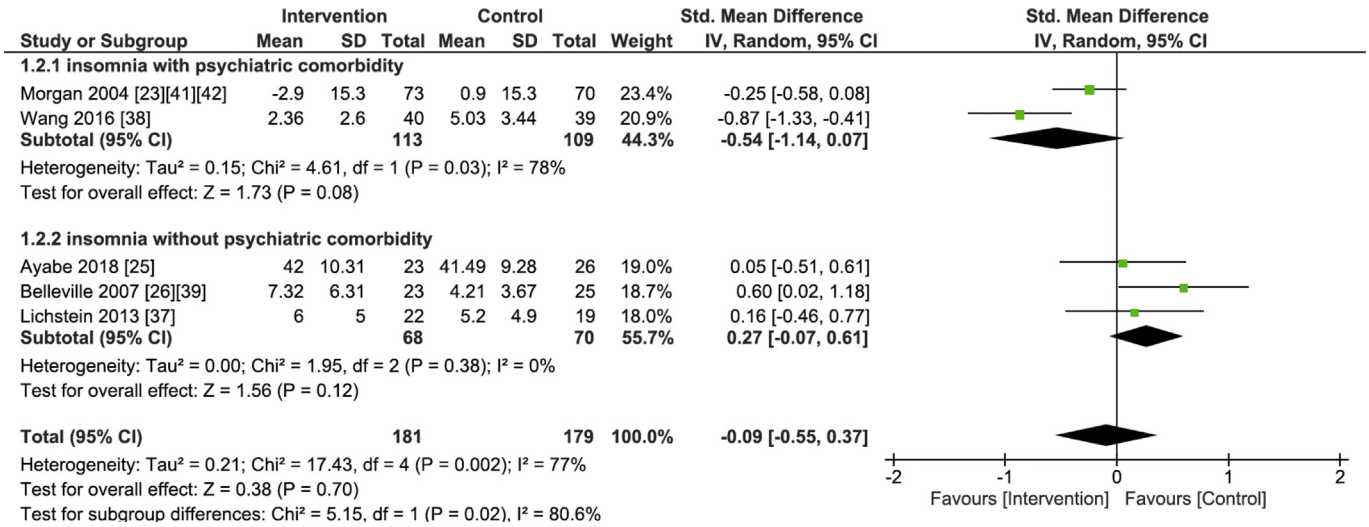

Fig. 5. Forest plot of post-intervention treatment effect sizes for daytime dysfunction. CI, confidence interval.

course of chronic insomnia [49]. A number of confounding factors may affect relapse of insomnia in the long-term course of chronic insomnia even after conducting CBT-I. With regards to the rate of discontinuation of BZDs over a long-term period, while some studies have observed significant effects with CBT-I [23,35,42], other studies have not found significant effects above and beyond that of gradual tapering alone [25,26,37,38]. Discrepancies in these results may be attributed to inadequate sample sizes. Another possible explanation may be that gradual tapering itself has a significant effect for reducing BZD hypnotics, but CBT-I plus gradual tapering could be more effective in discontinuing BZD hypnotics than gradual tapering alone. Of note, a previous systematic review indicated that gradual tapering was more effective than usual care for discontinuing BZD hypnotics in elderly patients with insomnia [16]. A study included in this systematic review reported that although CBT-I plus gradual tapering was effective in reducing insomnia symptoms and facilitating the discontinuation of BZDs in the long-term (12 mo), the statistically significant difference between CBT-I plus gradual tapering and gradual tapering alone over time [24]. The authors discussed that this gradual loss of between-group differences over time may have been due to the subject attrition rate or decreased adherence to the behavioral procedures in the combined intervention. They also suggested the necessity for "booster" sessions over time in order to maintain the effects of CBT-I for prevention of relapse in the long-term. Notably, another study included in this review, which utilized a "booster" session one month after the CBT-I, reported long-term effectiveness (12 mo) for discontinuation of BZDs [35]. Although the results of the subgroup

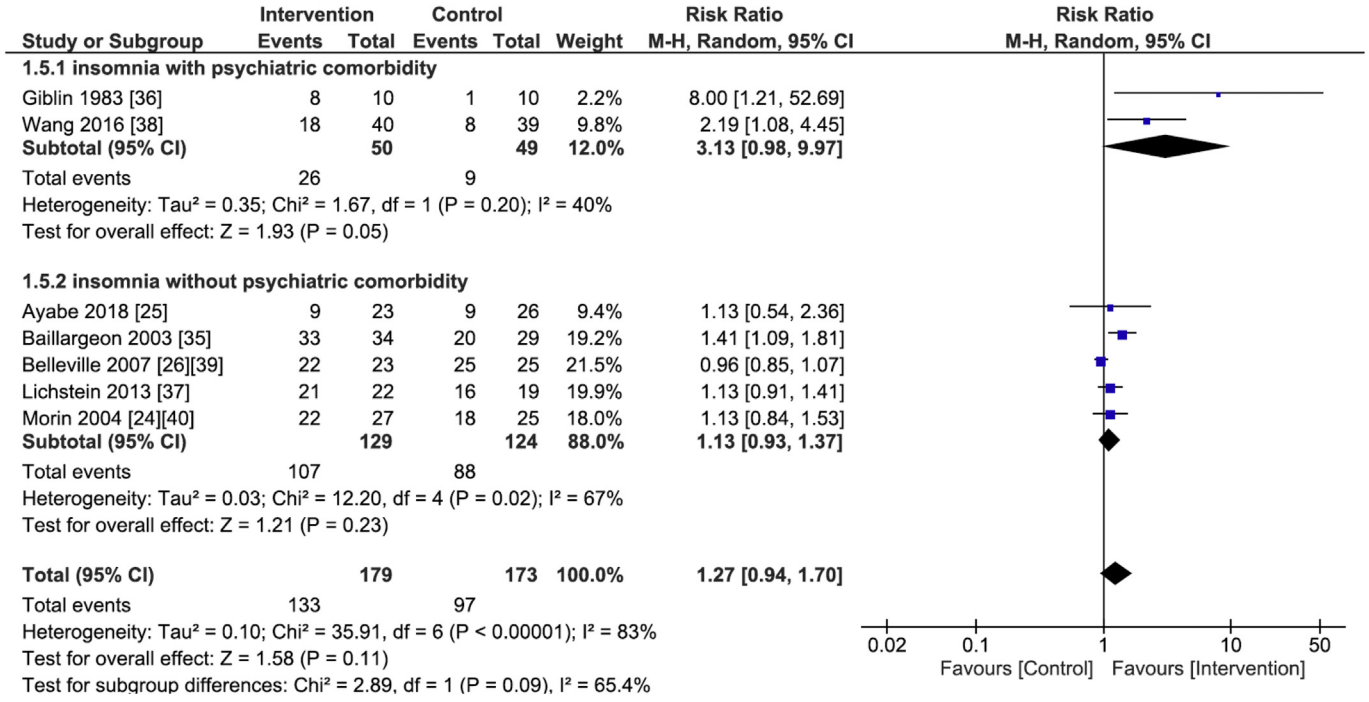

Fig. 6. Forest plot of post-intervention treatment effect sizes for a 50% reduction in the use of benzodiazepine hypnotics. CI, confidence interval.

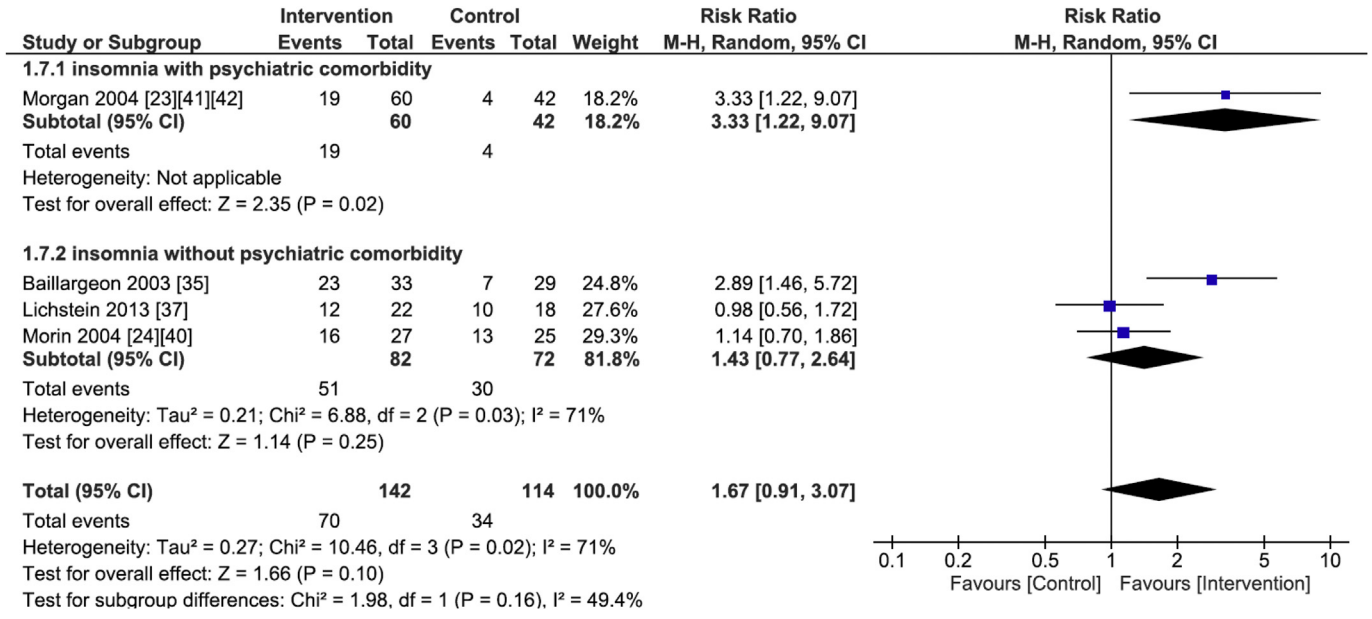

Fig. 7. Forest plot of the treatment effect sizes for the rate of discontinuation of benzodiazepine hypnotics at 12 mo post-intervention. CI, confidence interval.

analyses showed significant differences (between participants with chronic insomnia, with and without psychiatric comorbidity), with regard to long-term effects on insomnia symptoms and discontinuation of BZDs, the results need to be interpreted with caution due to the lack of statistical power and small sample size. Future studies with larger sample sizes and longer observation periods are required to fully evaluate the long-term effectiveness of CBT-I.

The results of our study revealed no significant differences in improvements in depressive symptoms between CBT-I and gradual tapering. The reported efficacy of CBT-I for treating depressive symptoms in patients with major depressive disorder was inconsistent across studies [50–55]. As several studies suggested, it is possible that the effects of CBT-I on depressive symptoms were not direct, but indirect effects mediated by improvements in insomnia symptoms [52,55,56]. Thus, the effects of CBT-I on depressive symptoms were uncertain depending on the differences in depressive symptoms, psychotropic medication, and psychosocial interventions. Our findings of the effects of CBT-I on depressive symptoms, which were highly heterogeneous among studies, are in line with such studies. A recent systematic review reported that CBT-I was effective for major depressive disorders comorbid with insomnia [50]. In contrast, most patients included in our review had mild depressive symptoms if any. This may explain the lack of effectiveness of CBT-I for depressive symptoms, as studies involving patients with moderate or severe depression were not included. Further research is required before a firm conclusion can be drawn regarding the efficacy of CBT-I in the treatment of depressive symptoms.

There were several limitations to our review. Firstly, the sample sizes across the included studies was relatively small, particularly for long-term studies. Further studies will be needed to clarify the long-term efficacy of CBT-I. Secondly, as responsiveness to CBT-I might be influenced by gender or age [57], it may have been advisable to conduct subgroup analyses on these variables. Such analyses, however, were not possible as the studies included in this review had similar distributions of gender and age. Thirdly, the interventions employed in the included studies varied widely, leading to a moderate to high heterogeneity of the results. Additional studies utilizing standardized protocols for intervention strategies, including gradual tapering, will be necessary to further

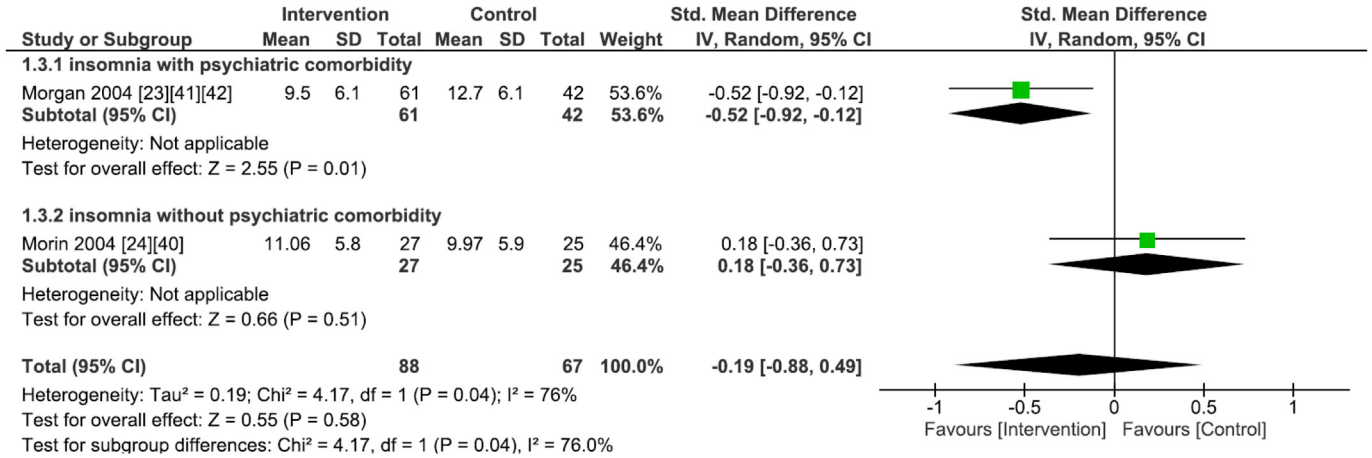

Fig. 8. Forest plot of the treatment effect sizes for improvement in subjective insomnia severity at 12 mo post-intervention. CI, confidence interval; SD, standard deviation.

delineate the potential effectiveness of CBT-I as a treatment option for discontinuing BZDs. Furthermore, our use of "50% reduction in the use of BZDs" as an outcome was based on previous studies that used this definition [23,35]. Nevertheless, most of these studies did not evaluate detailed patterns of BZD usage, and the lack of significant results in our study may have been attributed to the relatively low sensitivity of this outcome measure. Moreover, this review included only CBT-I as a psychosocial intervention because no RCTs have evaluated the effects of discontinuing BZDs using other psychosocial interventions. As such, there is a clear need for future RCTs to assess the effectiveness of alternative psychosocial interventions. Finally, the abovementioned relatively small sample size and moderate to high heterogeneity across the studies may limit the interpretability of the results.

Conclusions

Taken together, the results of our meta-analysis of RCTs indicated the significant effects of CBT-I in discontinuing BZD hypnotics as well as improving insomnia severity over a short-term period. Further studies with larger sample sizes and longer evaluation periods, including other psychosocial interventions, will be necessary to draw conclusions regarding the long-term efficacy of psychosocial interventions. Our results can aid physicians and patients who are willing to discontinue BZD hypnotics in the clinical setting.

Practice points

1) Current literature supports the effects of CBT-I together with a gradual tapering regime in discontinuing BZD hypnotics, as well as improving insomnia severity in the short-term.
2) Efficacy of CBT-I can be maintained up to 3 mo after the intervention, but long-term data is limited.

Research agenda

Future studies may include:

1) other psychosocial interventions.
2) long-term efficacy of psychosocial interventions.
3) dissemination and implementation studies examining the effectiveness of CBT-I for discontinuing hypnotics in clinical settings.

Conflicts of interest

Yoshikazu Takaesu has received lecture fees from Otsuka Pharmaceutical, Meiji Seika Pharma, Eli Lilly, Eisai, Mitsubishi Tanabe Pharma, MSD, and Yoshitomi Pharmaceutical, and has received research funding from Otsuka Pharmaceutical, Meiji Seika Pharma, MSD, and Eisai. Tomohiro Utsumi has received lecture fees from Eisai. Isa Okajima has received lecture fees from Otsuka Pharmaceutical, MSD, and Takeda Pharmaceutical, and has received research funding from NEC solution innovators. Akiyoshi Shimura has received personal fees from MSD and Meiji Seika Pharma. Nozomu Kotorii has received lecture fees from MSD and Eisai, and has received research funding from Otsuka Pharmaceutical, MSD, and Eisai. Kenichi Kuriyama has received speaker's honoraria from Otsuka Pharmaceutical, Meiji Seika Pharma, Eli Lilly, Eisai, Mitsubishi Tanabe Pharma, MSD, Yoshitomi Pharmaceutical, Sumitomo Dainippon Pharma, Janssen Pharma, and Takeda Pharmaceutical, and has received research support from Otsuka Pharmaceutical, Meiji Seika Pharma, MSD, Eisai, Takeda Pharmaceutical, Sumitomo Dainippon Pharma, Pfizer, and Kao. Masahiro Suzuki has speaker's honoraria from Eisai, Eli Lilly, Meiji Seika Pharma, MSD, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, and Pfizer. Norio Watanabe has received royalties from Sogensha, Medical Review, and Akatsuki for writings. Kazuo Mishima has received research support from the Japanese Ministry of Health, Labor, and Welfare and speaker's honoraria from Eisai and Takeda along with research grants from Eisai, Nobelpharma, and Takeda. Hidehisa Yamasita has no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.101214.

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