Reporting of Adverse Events in Cognitive Behavioural Therapy for Insomnia: A Systematic Examination of Randomised Controlled Trials

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Summary

Adverse events are undesirable events that can occur during medical or psychological treatment. There has been limited attention to adverse events in psychological treatment trials relative to pharmacotherapy trials. Cognitive behavioural therapy (CBTI) is the first line treatment for insomnia but studies have reported potential negative effects during acute implementation. This review aimed to understand the extent to which adverse events are monitored for and reported in the CBTI trial literature. Ninety-nine randomised controlled trials were identified for inclusion, with findings showing that 32.3% (n=32) of studies addressed adverse events in some way, while only 7.1% (n=7) of studies met all criteria for adequate reporting of adverse events. For studies that reported on adverse events by group, there did not appear to be differences between trial arms, however the limited evidence-base coupled with marked heterogeneity in monitoring and reporting makes it difficult to draw clear conclusions at this time. We outline recommendations for the field aimed at improving prospective monitoring and reporting of adverse events in psychological/behavioural treatment trials.

Keywords: Cognitive behavioural therapy; Insomnia; Sleep; Adverse events

Abbreviations: ASES, Asberg side effect scale; CBTI, Cognitive behavioural therapy for insomnia; CONSORT, Consolidated standards for reporting trials; Insomnia severity index, ISI; PTSD, Post-traumatic stress disorder; RCT, Randomised controlled trial; SRT, Sleep restriction therapy; TAU, Treatment as usual; TST, Total sleep time

Introduction

While psychological interventions are designed to benefit patients it is also possible that such treatments may have undesirable effects [1]. Historically, there has been limited attention given to this possibility, perhaps due to the assumption that talking therapy is inherently safer than pharmacological treatment. The term ‘adverse event’ is used to describe any negative event that occurs alongside treatment, which may include the development of new symptoms, an increase in existing symptoms, or deterioration in functioning [2, 3]. The causes of adverse events vary widely and include factors such as a treatment being applied inappropriately, or being applied correctly but to an incorrect presentation or patient group. The term ‘serious adverse event’ typically relates to events such as suicide attempts, deaths or hospitalisations [4].

The Consolidated standards for reporting trials (CONSORT) [5] recommend: 1) including clear definitions of adverse events alongside descriptions of any anticipated adverse events; 2) describing methods for monitoring and measurement, including whether validated measures were used and the timing of use; and 3) reporting any occurring adverse events alongside an attribution of the relationship to the intervention [5, 6]. In spite of existing guidelines, attention and scrutiny given to adverse events in clinical trials of psychotherapies is limited, especially in comparison to pharmacotherapies. In a systematic review of randomised controlled trials (RCTs) for mental health difficulties, 100% of the pharmacological trials mentioned possible or actual adverse events while just 60% of psychological intervention trials did so. In combined trials, adverse events were discussed at a higher proportion in the medication groups compared to the psychological intervention groups [7]. Another review of psychological interventions for various mental health difficulties revealed that 21% of included RCTs mentioned adverse events in some form,

while 3% fully reported measurement methods and 4% reported the occurrence of adverse events but without measurement information. In addition, 11% included information regarding deterioration and 3% briefly stated no occurrence of adverse events without further information [8]. Therapy for post-traumatic stress disorder (PTSD) was most commonly associated with monitoring for adverse events, possibly due to the use of exposure therapy, leading researchers to have a heightened awareness for adverse events. It is important to note that adverse events are not always associated with treatment; nevertheless, these events are important to record as it enables a more systematic evaluation of the relationship to intervention, and may reduce any bias towards attributing the events to external factors. In addition, it is recognised that these events may be inherent to the treatment and may even be essential for improvement to occur ('no pain, no gain'). However, they are still important to record because if an alternative intervention is found to have equivalent efficacy, but without negative events, this might become a preferable treatment.

Despite a strong evidence base, cognitive behavioural therapy for insomnia (CBTI) is not without potential for adverse events. For example, sleep restriction and stimulus control, both primary active components of CBTI, have been associated with decreased total sleep time (TST), increased sleepiness, and deterioration in functioning, specifically during the early stages of the treatment [9, 10]. In relation to sleep restriction, small uncontrolled studies have reported reductions in positive mood, alert cognition, and psychomotor vigilance during treatment relative to baseline [11, 12]. Furthermore, patients describe feelings of boredom and loneliness during extended wakefulness, as well as concerns regarding poor concentration and driving safety [9]. Indeed, one study found that subjective alertness was significantly lower in the CBTI group at post-treatment compared to those using Zopiclone [13]. In a study of people with comorbid insomnia and depression, those randomised to receive CBTI and antidepressant medication reported increased frequency of medication-

related side effects, and a greater burden associated with symptoms, in comparison to a group receiving medication plus sleep therapy placebo [14]. This may suggest that CBTI could exacerbate negative effects associated with medication when the treatments are administered in parallel.

One small study found a positive association between the presence of unwanted effects and improvements in sleep following sleep restriction. Although factors that contribute to this are unknown, it is possible that strict adherence to the protocol produces increased side-effects alongside improved outcomes [9]. The 'no pain, no gain' concept is relevant to CBTI, particularly for behavioural components that are designed to harness sleep drive – and by extension sleepiness – in order to reduce sleep latency and consolidate sleep [15]. However, some have argued that even in the case of treatment which often inherently involves negative experiences, removing avoidable adverse events is likely to improve treatment outcome [16]. Furthermore, there is an ethical responsibility to try and gain clarity about the nature and frequency of adverse events, since the lack of understanding of negative effects limits clinicians' ability to gain informed consent from patients. Information about anticipated negative effects also enables the management of expectations about the intervention, which has been found to increase treatment adherence [17, 18].

Current Review

Measuring and recording adverse events follows consistent standards in pharmacotherapy research. A move towards this in psychological treatment research, and specifically within CBTI, will enable the appraisal of both benefits and risks of treatment. It is first important to understand the extent to which monitoring and reporting of adverse events is already occurring within the CBTI literature in order to draw attention to this aspect of research, and to aid the development of recommendations. Here, we aimed to systematically review trials

of CBTI and examine them with respect to adverse event methodology by addressing the following questions:

1. To what extent do RCTs of CBTI report on procedures for monitoring adverse events within the methodology section?
2. How are adverse events defined in the CBTI literature?
3. What measurement methods are used to index adverse events in the CBTI literature?
4. To what extent do RCTs of CBTI report results of adverse events?
5. Is CBTI associated with higher rates of adverse events relative to control groups?

Design and Method

Search Strategy

Published studies were identified through the following allied health and medical databases: PsychInfo, CINAHL, Medline, EMBASE, AMED, and Cochrane. Databases were searched from inception until the 31st March 2019. Search terms included a range of terms relating to CBT, insomnia and randomised controlled trials. The following search terms were used: "cognitive behav* therap*" or "cognitive behav* intervention" or "cognitive therap*" or "behav* therap*" or "behav* modification" or "CBT" or "CBT-I" or "ICBT" or "sleep hygiene" or "stimulus control" or "relaxation" or "sleep restriction" or "psychotherap*" AND "insomnia*" or "chronic insomnia" or "sleeplessness" or "sleep disord*" or "sleep initiation" or "sleep maintenance" or "poor sleep*" or "sleep* problem*" or "sleep disturbance" AND "RCT" or "randomi?ed control* trial" or "control* trial" or "intervention trial*" or "clinical trial*". The bibliography of a recent meta-analysis of CBTI was also hand searched [19]. Titles and abstracts were screened by the author (HC); for studies indicating possible eligibility, a full text version was acquired to allow for further eligibility screening. Where

there was a query, a second author (SK) reviewed the paper and an agreement was made regarding eligibility.

Inclusion and Exclusion Criteria

Papers were included if they were peer reviewed and written in English. Inclusion criteria were: i) published between 1980-March 2019; ii) using an adult sample (≥18 years) with insomnia disorder, diagnosed using either research or clinical diagnostic criteria; iii) a RCT design; iv) the intervention was CBT delivered in any modality targeted at treating insomnia (including at least 2 of the commonly used components: sleep hygiene (psychoeducation), cognitive therapy, stimulus control, sleep restriction, or relaxation therapy) with no stipulation for there to be a combination of cognitive and behavioural components; v) comparison with a non-active control group (e.g. placebo, waitlist), treatment as usual (TAU) or a minimally-active intervention such as sleep hygiene education.

Studies where participants had comorbid psychiatric or physical health diagnoses alongside insomnia were included as long as the treatment was specifically targeting insomnia. Studies where the CBTI intervention had been minimally adapted for delivery with a comorbid disorder were also included if the treatment maintained a principal focus on sleep difficulties.

Studies were excluded if: i) they were published prior to 1980; ii) the primary focus of the CBTI intervention involved tapering of medication; iii) the CBTI protocol was combined with an adjunctive treatment (e.g. CBTI combined with medication or CBTI combined with light therapy) or if the CBTI was combined with another therapy model (e.g. mindfulness-based cognitive therapy); iv) the CBTI protocol was combined with a treatment for another disorder (e.g. CBTI and pain) AND the treatment appeared to target both difficulties; v) they involved secondary analyses or follow up data of a parent or primary study.

Data Extraction and Data Synthesis

Details of the included studies were recorded by the first author (HC) using a data extraction form. Data regarding concepts such as adverse events, unwanted outcomes, side effects, negative consequences, harm, safety, or tolerability were extracted. Data regarding outcomes such as dropout, adherence, and increases or decreases on symptom measures were not extracted as adverse events data unless the author of the paper made a clear link between these outcomes and negative effects. This is because such outcomes may be collected in RCTs without the intention of monitoring for or drawing conclusions about adverse events in treatment, and the current review aims to understand the extent to which adverse events are specifically and purposefully monitored for.

In order to understand the extent to which published RCTs measure and report adverse events, studies were assessed along five dimensions and assigned a score of one if each of the following were present: i) stating that adverse events would be measured or monitored for as a potential outcome within the methods section of the paper; ii) pre-defining what would be classified as adverse events; iii) reporting the method of measurement or monitoring of adverse events; iv) reporting the time point(s) when adverse events were assessed; v) reporting occurrences or outcomes of adverse event assessments in the results. Each paper was assigned a total score between zero and five, with higher scores indicating better reporting of adverse events. Where studies had monitored for and reported adverse events in a medication arm but not in the CBTI arm, the study was given a score of zero.

Results

Identification of Studies

Electronic searching identified 2790 results, while hand searching identified a further nine studies. Once duplicates were removed, 1779 citations were screened for inclusion. Following the review of titles and abstracts, 277 citations remained. After applying inclusion/exclusion criteria to full-text papers, 99 papers were retained for inclusion in the review (see figure 1).

Study Characteristics

For details of all included studies please see table S1 in the supplementary material along with associated references. A small proportion of the included studies were published before 2000 (n=6; 6.1%), 28% were published between 2000-2009 and the majority were published between 2010-2019 (n=65; 65.7%). Of these studies, the majority were published within North America (n=53; 53.5%) and Europe (n=31; 31.3%), with a small amount published in Asia (n=9; 9.1%) and Australasia (n=6; 6.1%).

Sample sizes varied widely, ranging from 17 participants to 3755 participants. The total number of participants across all included studies was 15,967, with 8246 of these participants allocated to CBTI and 7201 to control. Studies predominantly recruited via the community (n=50; 50.5%), with a large proportion of studies recruiting through specialist, secondary or tertiary settings, such as hospitals, specialist clinics and mental health services (n=27; 27.3%). A smaller number recruited through primary care settings (n=8; 8.1%). Some studies recruited from two or more settings (n=9; 9.1%); six of which recruited from both a specialist care setting and the community, two recruited from primary care and the community, and one

recruited from all three settings. A small number of studies also recruited specifically through universities (n=2; 2.0%) and workplace settings (n=3; 3.0%).

Adverse Event Monitoring and Reporting

Across studies, 32.3% (n=32) addressed adverse events in some way i.e. scored positive on at least one of our five pre-defined reporting criteria (see table 1 for studies scoring ≥1 and details of which criteria were met). Thus, the vast majority (67.7%) did not address adverse events at all. The most frequent aspect of reporting (31.3% of studies) reflected stating in the results section whether adverse events occurred, yet the majority of these studies (53.1%) did not specify a methodology for the definition or collection of adverse events. Importantly, only 7.1% of studies met all of our adverse events reporting criteria (i.e. a score of 5; see table 1).

Question 1: Reporting adverse events in study methodology

Seven studies (7.1%) described the measurement or monitoring of potential adverse events in the methodology section. Six of these studies [20-25] described this information within the measurement and outcome sections of the methodology, and one described this within the treatment delivery section [26].

Question 2 and 3. Definition and measurement of adverse events

Given the limited demarcation between how studies defined and measured adverse events, these two domains will be described together. Ten studies (10.1%) predefined what would be considered an adverse event prior to reporting any occurrence of adverse events, and fifteen studies (15.2%) described the methods for the measurement or monitoring of adverse events. Of these 15 studies, seven described their measurement approach in the methodology section,

while a further eight studies revealed their measurement approach later in the paper, typically in the results sections. It was noted that across studies there was often no clear distinction between events that would be considered as *serious* adverse events and those that may be considered as side effects or negative effects, and many terms were used interchangeably between studies. Due to this, we have not separated out our reporting of adverse events in the literature and have only described events as serious adverse events where that was stated in the original text.

For the ten studies that detailed definitions of adverse events, all of them also included measurement information. Of these ten, three defined adverse events as deterioration in sleep post-intervention, with two utilising the insomnia severity index (ISI) [27] score at post-treatment [28, 29], and another using sleep diary data at both post-treatment and follow-up [30]. One of these studies additionally asked every participant who dropped out whether any adverse events had occurred [28], however, this method did not appear to be used with treatment completers.

Five studies defined adverse events by listing specific events that would be classified as adverse events. Of these studies, three included suicide attempt or death [20, 21, 25] and four included hospital admission [20, 21, 24, 25]. Two studies also included violent incidents and formal complaints about the intervention [20, 21]. One study described events such as falls, accidents or any other negative physical or psychological event related to sleepiness or fatigue [22]. Many of these studies described participants being able to report adverse events or concerns with treatment at any point during the study and stated that any reports of adverse events would be recorded [20, 21, 25, 31, 32]. One study stated that participants were asked about adverse events over the duration of the study and at follow up [22]. Additionally, Freeman et al. [20] also reported that medical notes were checked at the end of the study.

One study investigating people with a diagnosis of bipolar disorder also classified manic or depressive episodes and relapse as adverse events, alongside sleepiness and dropout monitored via the completion of weekly self-report [24]. Specifically, they utilised the Young mania rating scale [33], the Quick inventory of depressive symptomology – self report [34] and the Epworth sleepiness scale [35].

Two studies defined what would be considered an adverse event by using either their own rating scales or standardised rating scales. Specifically, Espie et al. [23] classified adverse events via a symptom checklist, administered eight weeks post-randomisation [9] . This is a 14-item measure which asks participants to answer questions about whether participating in treatment resulted in a list of symptoms across somatic and psychological domains, such as low mood, fatigue/exhaustion, headache/migraine, extreme sleepiness, reduced motivation/energy and feeling irritable. Level of interference with daily functioning is also measured. As this is a relatively new tool, it has not been utilised widely within the CBTI literature. However, it is structured similarly to checklists assessing for adverse events in pharmacological trials [36, 37] but has the advantage of being specifically developed with a focus on adverse events that may occur within CBTI. Germain et al. [26] defined adverse events via the Asberg side effect scale (ASES) [36] which includes items such as physical tiredness, 'orthostatic symptoms' such as feeling lightheaded or fainting, sleep disturbance, headache and dizziness. The authors reported that clinicians assessed adverse events weekly via the use of patient self-report [26], guided by the ASES [36].

A further five studies provided information on measurement methods without defining what adverse events were being monitored for. This included two studies reporting that participants were monitored closely throughout the trial by staff, but there was no further detail on methods or timepoints [38, 39]; and one study stated that therapists monitored for

adverse events by asking participants whether they had encountered any problems since their last session [40]. Two studies briefly stated that participants could contact staff at any time during the study to report adverse events [31, 32].

Question 4. Adverse event results

In total, 31 (31.3%) studies reported adverse event results. However, as some studies included more than one CBTI arm we report on 36 CBTI intervention groups, reflecting individual face-to-face intervention (n=16), online intervention (n=11), group intervention (n=7) and self-help intervention (n=2).

Question 5. Rates of adverse events in CBTI

While 31.3% of included studies met criteria for reporting adverse event results, the way in which studies reported findings varied widely. In particular, there were varying levels of clarity about whether formal comparisons between intervention and control groups had been made. In several studies, authors reported that no adverse events had occurred or that none were reported during the study [21, 31, 39, 41-48]. Although it is possible that this represents a rate of zero in each trial arm, it is difficult to be sure when there is no specific reference to the separate groups. Additionally, a number of studies reported that there were no adverse events in relation to treatment, but did not specify rates in the control group [22, 40, 49-53]. In one of these studies, the authors noted that there were no adverse events "related to the intervention or trial" [22]; again, it is likely that this represents a rate of zero in each group, but specific mention of the control group would bring further clarity. One study reported no serious adverse events in relation to treatment, and two adverse events (dyspnea after a meal and an episode of mild depression due to discontinuation of medication) in the treatment arm but did not report corresponding rates for the control group [38].

When rates for each group were specified, four studies briefly stated that no adverse events had occurred in either group without further detail on what would have been considered an adverse event or how they were monitored for [54-57]. Where adverse events did occur and rates were reported between groups, eight studies reported either no significant difference between groups or that adverse events were not clinically meaningful or were unrelated to the study [24-26, 28, 29, 58-60] and two studies reported significant differences between groups [23, 30]. See supplementary table S2 for details of these 10 studies.

Two studies reported significant differences between trial arms. One study compared the proportion of each group exhibiting deterioration in sleep and presented this information for those taking/not taking sleep medication. The general pattern was that the waitlist group were more likely to exhibit deterioration in sleep than self-help or therapist-led treatment [30]. The second study reported significantly higher rates of adverse events (defined as endorsed symptoms attributed to the sleep intervention) in the digital CBTI arm compared to a sleep hygiene education control [23]. Participants in the intervention group were significantly more likely to report the following symptoms: extreme sleepiness, fatigue or exhaustion, attention and concentration problems, low motivation and energy, headaches, memory difficulties and irritability in relation to taking part in the intervention.

Discussion

Summary of Findings

Extent and patterning of adverse events reporting in the literature

The chief finding from this review is that published trials of CBTI have paid limited attention to the measurement and reporting of adverse events. The majority of trials did not mention adverse events at all, while 32% of studies addressed adverse events in some way. Of these,

many provided a cursory summary in the results section without providing adequate details on how adverse events were defined or measured. Critically, only a small number (just 7.1% of studies) met all of our criteria for reporting adverse events.

Encouragingly, it appears that attention to adverse events may be improving over time, perhaps due to increased emphases in guidelines and the broader psychological treatment literature [5, 17]. For example, of all the studies addressing adverse events in some way (n=32), over half were published between 2015 and 2019 (n=19). Furthermore, the seven studies that met all adverse events criteria were published after 2011, with five being published in the last five years.

In addition, it appears that the presence of comorbidities may be associated with improved monitoring of adverse events. Indeed, a large proportion of studies addressing adverse events were represented by studies either specifying limited exclusion criteria for comorbidities, or specifically recruiting participants with physical or psychiatric comorbidities. Of the seven studies meeting all specified adverse events criteria, CBTI was investigated in people with psychosis [20], bipolar type I [24], and depression [22, 25], as well as three studies that declared they did not exclude physical or psychiatric comorbidities [21, 23, 26]. It is possible that better reporting is due to heightened awareness of the potential for adverse events when working with populations in which there is a possibility of exacerbating existing difficulties.

Definitions and measurement methods used

Despite the relatively low number of studies addressing adverse events, several studies stood out as examples in which definitions of adverse events were present and defined clearly. This included listing specific incidents that were considered adverse events and serious adverse

events [20-22, 25], or measuring deterioration of comorbid mental health difficulties [21, 24], worsening sleep [28-30] and self-reported treatment-related symptoms [23, 26].

The description of measurement methods ranged in clarity, with some studies simply stating that participants had the opportunity to report adverse events during the intervention or that adverse events were monitored by staff, but with no further description of how this actually took place. Where study procedures were reported, this involved asking participants about adverse events [22]; checking medical records [20]; using standardised tools to measure outcomes such as deterioration of comorbid symptoms or sleep [21, 24, 28-30]; completing clinical assessments guided by side effect measures; or administering CBT-tailored checklists of adverse events [23, 26].

Rates of adverse events in CBTI in comparison to control groups

Where results were reported, variation in measurement and lack of consistency in reporting render it difficult to draw firm conclusions regarding the association of adverse events with CBTI in comparison to control groups. For example, many studies did not distinguish between serious adverse events and more minor adverse events. In studies where serious adverse events were defined, they did not appear to be attributed to CBTI or show increased frequency relative to controls groups.

The majority of studies found no difference in adverse events between groups, however for several of these studies the definition and measurement approach was not evident; and for others it was not always clear whether between-group differences were compared statistically or just descriptively. Furthermore, where adverse events occurred but were not related to the intervention, the process for determining this relationship (and by whom) was not typically described. This lack of clarity in many studies, alongside variation between studies, leads to the possibility that adverse events may have occurred but were not measured, identified, or

reported. This means that any comparisons between trial arms will be limited until a more consistent method of monitoring and reporting is implemented.

In addition, heterogeneity in type of adverse event makes it difficult to generate clear conclusions. For example, one study defined adverse events as deterioration in sleep and - perhaps unsurprisingly - found increased rates in the control group versus CBTI [30]. In contrast, a study reporting on self-attributed side effects of sleep intervention found an increased rate of adverse events in the CBTI group versus sleep hygiene [23]. It should be noted that this study is the largest study (n=1711) to date to assess adverse events in a structured manner across both trial arms. Synthesis of rates across studies will not be possible until enough studies implement consistent measurement and reporting. On a related point, methodology for monitoring adverse events may also yield different results. For example, previous findings in pharmacological studies suggest that methods such as checklists and self-report ratings are associated with higher rates of reporting adverse events compared to unstructured assessments [61]. This may be because participants do not spontaneously report particular symptoms as treatment-related until specifically asked [62]. Alternatively, in the case of measures such as the symptom checklist [9], it is possible that answers may reflect, to some extent, reporting of ongoing symptoms of insomnia, such as fatigue or lack of motivation, rather than new-onset symptoms or increased exacerbation of existing symptoms since the commencement of treatment. Researchers should seek to clarify the attributional nature of questionnaire items when administering adverse event assessments. The combination of open reporting and specific measures is likely to generate the most beneficial results. For example, encouraging participants to openly report serious adverse events, alongside more active or structured measurement of mild adverse events, may be a helpful procedure even if the reported events are eventually determined to be unrelated to the treatment.

Implications

Our review shows there is limited monitoring and reporting of adverse events in CBTI trials. This may be due to historical assumptions that psychological treatments cannot engender harm [63], as well as a lack of standardised methodology for monitoring and reporting adverse events in insomnia research. Should reporting become a more reliable feature of future research, it may be possible to understand whether CBTI is reliably associated with adverse events, and whether such events are related to factors such as patient or therapist characteristics or treatment delivery protocols. Indeed a recently published study [64] compared cognitive therapy with behaviour therapy (SRT, stimulus control, sleep hygiene) using the aforementioned symptom checklist [9]. Results showed that a greater proportion of patients in the behaviour therapy group (43%) reported treatment-attributed adverse events compared to the cognitive therapy arm (14%), with group differences being particularly pronounced for "fatigue/exhaustion" (33% vs. 4%) and "extreme sleepiness" (25% vs. 0%).

A logical conclusion from our review is that adverse events are unlikely to be well understood, or indeed discussed with patients in clinical practice. Theories of health behaviour suggest that patients are motivated to complete treatment and tolerate difficult aspects/ overcome obstacles if they are given adequate information about the treatment, alongside strategies to cope with challenges to engagement [18]. However, such cost-benefit discussions are likely to be lacking in clinical settings given the limited evidence base in the literature. Should adverse events become a better understood part of CBTI, clinicians may consider planning-in extra time during initial sessions in order to discuss possible negative effects of treatment, to manage treatment expectations as well as problem-solve possible barriers to engagement. Regular review over the course of treatment may also help structure and tailor support when needed. From a research perspective, it may also be fruitful to

develop and test strategies to mitigate minor adverse events (e.g. countermeasures against fatigue and sleepiness) and improve patient adherence/engagement.

Limitations

The current review only included studies where CBTI was compared to a non-active or minimal intervention control group. This was in order to facilitate comparison across studies when considering differences in adverse events between intervention and control groups. Future work is needed to assess rates of adverse events across different treatment modalities. Additionally, the current study only extracted data where a clear link to adverse or negative effects was drawn by the authors. This meant that data regarding factors such as drop out, symptom deterioration or events such as hospitalisations were not extracted unless it was defined or reported as an adverse event. In addition, data on the definition of adverse events were only extracted if the study predefined what was classified as an adverse event prior to reporting results. Some studies reported detail in the results section that gave an indication of the type of events considered 'adverse', such as one study reporting that a participant had a minor depressive episode or experienced dyspnoea [38]. Finally, we utilised a binary scoring system to appraise each trial, whereby studies were assigned a score for meeting criteria regardless of level of detail provided. Therefore, conclusions made by this review are limited to the extent – rather than quality – of adverse event reporting.

Recommendations

A clear implication of the current review is that CBTI trials should attempt to monitor for the occurrence of adverse events and serious adverse events in a clear and explicit way in order to facilitate replicability and comparison across studies. Importantly, authors should monitor

for and report adverse events consistent with CONSORT guidelines [5]. The following recommendations may also be beneficial for CBTI trialists to consider:

- When defining adverse events, consider potential adverse events such as deterioration on outcome measures, worsening of sleep, increase in comorbid mental or physical health difficulties, reported symptoms attributed to CBTI, or drop out (and associated reasons) from intervention.
- When defining serious adverse events consider outcomes such as death, suicide attempt and hospitalisation. This may also include events such as readmission to a secure inpatient unit if the population is experiencing comorbid mental health difficulties.
- When describing data collection methods, describe the reliability and validity of the tools used. Where new tools have been developed, describe the rationale for development and item inclusion.
- Consider active measurement of mild adverse events as these may not be spontaneously reported, particularly if they are similar to insomnia-related symptoms. For example, the use of a checklist of CBTI-related adverse events may facilitate formal assessment of mild adverse events [9].
- Distinguishing between the symptoms of insomnia and adverse events during treatment may be a challenge for both patients and researchers. When asking patients to report adverse events, it may be beneficial to explicitly instruct and remind patients that these would be symptoms which have occurred or increased since the commencement of treatment.
- When reporting the results, clearly describe the rates of adverse events in each trial arm.

- Provide details about the process for which the relationship of adverse events to intervention was determined. For example, in the occurrence of serious adverse events one might collect information about whether the intervention had been implemented at the time of serious adverse events, whether it abated when the intervention was ceased, and whether it reappeared following reintroduction of the intervention.
- Describe the role and independence of the person who has responsibility for deciding the relationship between adverse events and the intervention.

Conclusion

Overall, this review highlights a current lack of attention to adverse events in trials of CBTI, with the exception of a small number of studies. The extent to which adverse events were addressed varied in relation to different features of reporting, with fewer studies addressing and defining adverse events in the methodology and a comparatively larger amount discussing results of adverse events, albeit very briefly. In addition, methods of monitoring, types of adverse events monitored for, and the quality of reporting varied widely. This meant that conclusions regarding frequency of adverse events in CBTI arms compared to control groups could not be drawn based on current data. There is a clear need, therefore, for more consistent and transparent monitoring and reporting of adverse events in CBTI trials. This will enable future systematic examination of risks and benefits of specific treatment strategies; and support clinicians to engage patients in informed discussions about treatment, support patients to overcome potential difficulties, and ultimately improve care for those undertaking psychological treatment for insomnia.

Practice points

- CONSORT guidelines recommend that adverse events should be measured and reported in randomised controlled trials of psychological treatments.
- Although CBTI has been associated with some negative effects, there appears to be a lack of monitoring for and reporting of adverse events in the literature.
- Where adverse events are discussed, variation in definition, measurement methods and detail in reporting mean that conclusions regarding the occurrence of adverse events in CBTI cannot be drawn at present.

Research Agenda:

- Future trials of CBTI should follow CONSORT guidelines for monitoring and reporting adverse events.
- Active measurement of mild adverse events during CBTI may elicit symptoms that would not be spontaneously reported. Studies should aim to understand if mild adverse events vary by treatment-related factors (e.g., component composition, delivery method, therapist background) and patient-related factors (e.g., comorbidities, medication use, sleepiness, degree of subjective-objective sleep discrepancy).
- Future studies should consider the challenges of distinguishing between adverse events and symptoms of insomnia.

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Tables

Table 1. Pattern of adverse event reporting for studies scoring ≥ 1 following structured assessment (n=32 out of 99 reviewed studies)

	Scoring criteria (✓ indicates criteria met)					
Study	Total Score	adverse events in methods [1]	adverse events defined [2]	adverse events measurement [3]	adverse events measurement time points[4]	adverse events results[5]
Alessi et al. (2016) [54]	1	-	-	-	-	✓
Bothelius et al. (2013) [41]	1	-	-	-	-	✓
Buysse et al. (2011) [42]	1	-	-	-	-	✓
Chen et al. (2008) [38]	2	-	-	✓	-	✓
Chen (2011) [51]	1	-	-	-	-	✓
Christensen (2016) [55]	1	-	-	-	-	✓
Duman & Taşhan (2018) [43]	1	-	-	-	-	✓
Espie et al. (2007) [56]	1	-	-	-	-	✓
Espie et al. (2008) [57]	1	-	-	-	-	✓
Espie et al. (2012) [44]	1	-	-	-	-	✓
Espie et al. (2019) [23]	5	✓	✓	✓	✓	✓
Freeman et al. (2015) [20]	5	✓	✓	✓	✓	✓
Freeman et al. (2017) [21]	5	✓	✓	✓	✓	✓
Germain et al. (2012) [26]	5	✓	✓	✓	✓	✓
Hagatun et al. (2019) [31]	3	-	-	✓	✓	✓
Harvey et al. (2015) [24]	5	✓	✓	✓	✓	✓
Jernelov et al. (2012) [53]	1	-	-	-	-	✓

Lancee et al. (2015) [28]	4	-	✓	✓	✓	✓
Lancee et al. (2016) [29]	4	-	✓	✓	✓	✓
McCrae et al. (2007) [45]	1	-	-	-	-	✓
Morawetz et al. (1989) [30]	4	-	✓	✓	✓	✓
Sadler et al. (2018) [39]	2	-	-	✓	-	✓
Sandlund et al. (2017) [32]	1	-	-	✓	-	-
Sivertsen et al. (2006) [60]	1	-	-	-	-	✓
Smith et al. (2015) [59]	1	-	-	-	-	✓
Smitherman et al. (2016) [46]	1	-	-	-	-	✓
Soleimani et al. (2015) [49]	1	-	-	-	-	✓
Taylor et al. (2017) [40]	3	-	-	✓	✓	✓
Van der Zweerde et al. (2019) [22]	5	✓	✓	✓	✓	✓
Watanabe et al. (2011) [25]	5	✓	✓	✓	✓	✓
Yamamoto et al. (2016) [50]	1	-	-	-	-	✓
Zachariae et al. (2018) [47]	1	-	-	-	-	✓

[1] The study discussed adverse events within the methods section of the paper.

[2] The study predefined the outcomes that would be classified as adverse events.

[3] The study provided detail on the methods of adverse events measurement or monitoring

[4] The study described the timepoints of adverse events measurement or monitoring

[5] The study discussed the outcome or results of adverse events measurement or monitoring