

ORIGINAL ARTICLE

Can people with poststroke insomnia benefit from blended cognitive behavioral therapy? A single case experimental design

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Abstract

Purpose: Sleep is essential for our overall health and wellbeing. Unfortunately, stroke often induces insomnia, which has been shown to impede rehabilitation and recovery of function. Cognitive behavioral therapy for insomnia (CBT-I) is the treatment of choice for insomnia in the general population and is efficacious both when delivered face-to-face or online. The primary aim of this study was to evaluate efficacy of blended CBT-I (eCBT-I) in five poststroke participants with insomnia according to DSM-5 criteria.

Methods: A randomized multiple baseline design was used to evaluate improvements in total sleep time, sleep onset latency, sleep efficiency, nocturnal awakenings and sleep quality. The intervention included six weeks of eCBT-I combined with two face-to-face sessions.

Results: All participants completed the intervention. One participant stopped using the diary, while the other four completed it fully. All five sleep diary measures improved, significantly so for nocturnal awakenings. Moreover, after completion of the treatment, four out of five participants no longer fulfilled DSM-5 criteria for insomnia disorder

Conclusions: This is the first study to show that blended CBT-I is potentially effective in participants with post-stroke insomnia. The findings justify extension to a randomized controlled trial.

Keywords: cognitive behavioral therapy; sleep; eHealth; acquired brain injury; rehabilitation; stroke; insomnia

Introduction

There is an increasing awareness that insomnia is common following a stroke. A recent meta-analysis found a pooled prevalence estimate of 32.21% (CI 18.5–47.64) in six studies using DSM-IV or DSM-5 criteria for insomnia (Baylan et al., 2020). These criteria include difficulty initiating or maintaining sleep or waking up early. To reach a diagnosis of insomnia disorder, sleep difficulties should occur at least three nights a week and should be present for at least three months. People with insomnia are at risk of mental health problems, as well as overall health concerns. They have a decreased quality of life, higher rates of work absenteeism, and are more prone to accidents (Daley et al., 2009; Roth, 2007). In individuals with a stroke, insomnia is associated with more severe physical disabilities, pain, neuropsychiatric disturbances, and cognitive

impairments (Baylan et al., 2020; Leppavuori, Pohjasvaara, Vataja, Kaste & Erkinjuntti, 2002). Furthermore, poor sleep may complicate recovery processes in the acute phase (Duss et al., 2017), and motor learning in the acute and chronic phase following stroke (Siengsukon & Boyd, 2009). Given the high prevalence and negative consequences, it seems clear that treatment of insomnia should be an important part of stroke rehabilitation.

In the general population, cognitive behavioral therapy for insomnia (CBT-I) is recommended as a first choice treatment in guidelines (Qaseem, Kansagara, Forcica, Cooke & Denberg, 2016; Riemann et al., 2017). There is growing evidence for the efficacy of CBT-I in specific populations as well, such as cancer (Johnson et al., 2016), pain (Jungquist et al., 2010), psychiatric disorders (Taylor & Pruiksma, 2014), and traumatic brain injury (Nguyen, McKay, et al., 2017; Ouellet & Morin, 2007; Theadom et al., 2017). Only three studies so far have examined the efficacy of face-to-face CBT-I in a stroke population. Herron, Farquharson, Wroe & Sterr (2018) found in a single-case experimental design in five stroke patients improvements on two or more sleep parameters, and three participants no longer met diagnostic criteria for insomnia posttreatment and at 2-week follow-up (Herron et al., 2018). Their seven sessions intervention consisted of CBT-I, extended with additional management strategies for the consequences of stroke. Nguyen et al. (2017) found in a pilot randomized controlled trial with 15 participants significant improvement after eight sessions CBT-I on sleep quality and insomnia severity, compared to treatment as usual (Nguyen, Wong, et al., 2017). Improvement of sleep quality remained at 2-month follow-up, and insomnia severity was no longer superior to usual treatment. The CBT-I protocol in their study was extended with fatigue management strategies. Ymer et al. (2021) built on the findings of Nguyen et al. (2017), and conducted a randomized controlled trial in 51 participants with acquired brain injury (stroke $n = 29$, traumatic brain injury $n = 22$) comparing eight sessions of CBT-I for sleep disturbance and fatigue (CBT-SF) with eight sessions of health education to control for non-specific therapy effects (Ymer et al., 2021). Participants of the CBT-SF group reported significantly greater improvements of sleep quality at posttreatment and 2-month follow up, compared to the participants receiving health education. These findings suggest that CBT-I is a promising treatment option for poststroke insomnia.

In this pilot study, we tested a newly developed blended *online* CBT-I (eCBT-I), adjusted for people with acquired brain injury. Participants complete this online program largely on their own, with a therapist providing written feedback online. In the general population, availability of face-to-face CBT-I is limited for different reasons, including a lack of trained therapists (Ritterband et al., 2009). Offering a (partly) online intervention may help to disseminate treatment better (Zachariae, Lyby, Ritterband, & O'Toole, 2016). Clear explanations of intervention are provided online, with specific feedback tips for therapists on homework assignments. Online CBT is an effective treatment for people with insomnia (Seyffert et al., 2016; Zachariae et al., 2016), easier to access and feasible for people with traumatic brain injury (Theadom et al., 2017). A potential additional benefit of eCBT-I for people with stroke and cognitive deficits is the opportunity to reread the information at their own time and pace, following the structured treatment protocol. The online treatment is blended with face-to-face sessions to optimize treatment adherence and to coach the patients to use the online tool. This is the first study evaluating blended eCBT-I in participants with a stroke.

Aims

The present study examined the effect of blended eCBT-I on sleep in patients with post stroke insomnia. We also explored the effects on fatigue, emotional well-being, cognitive functioning, and societal participation as insomnia in stroke is associated with those factors (Baylan et al., 2020).

Methods

Design

The study was designed to meet, as far as possible, the standards for the methodology of single case experimental designs (Dugard, File & Todman, 2012; Kratochwill *et al.*, 2013; Tate *et al.*, 2015), and the report was prepared according to SCRIBE criteria (Tate *et al.*, 2016). A randomized non-concurrent multiple baseline design across subjects (Dugard *et al.*, 2012) was applied to sleep diary data to examine the effect of intervention on sleep. For practical reasons, a concurrent design, in which the baseline commenced at the same point in time, was not feasible. Instead baseline measurements started non concurrently during a two-month period. However, as the same intervention was sequentially applied to different participants with similar characteristics in the same setting, data of participants were combined in order to improve internal validity. Each individual served as his or her own control. The start of the intervention phase was determined randomly, by using a research randomizer program (www.randomizer.org), given the restriction that the baseline period should last at least 7 days and at most 3 weeks (21 days). The minimum length of 7 days was set to get a reliable estimation of the sleep disturbances as these may differ per night. Theoretically, the intervention could start on any day between the 8th and 21st days, resulting in a total of 14 possible starting points for intervention. Participants completed daily measurements during baseline phase (1–3 weeks), intervention period (fixed length of 6 weeks), posttreatment (1–3 weeks) and after 6 weeks again for follow-up (1 week). Secondary outcome measurements were collected at the beginning of the baseline period, posttreatment at the end of intervention and at 6-week follow up. See Table 1 for an overview of measurement time points for all participants.

Participants

A total of 11 outpatients diagnosed with a stroke were seen by a rehabilitation team in an 8-weeks period, of which five patients reported complaints with their sleep and scored above clinical cutoff on the Insomnia Severity Index (Morin, Belleville, Bélanger & Ivers, 2011). These five patients were invited to participate in the study, and all agreed and met eligibility criteria. Inclusion criteria were a history of a stroke (confirmed by data from CT or MRI in medical record), insomnia disorder according to DSM-5 criteria, aged 18 or older, and capable of using internet. Ability to use the internet was determined by both the availability of devices and recent experience with online activities such as email. Exclusion criteria were severe cognitive impairments which made them unable to use the online treatment (such as severe aphasia), unstable medication regimens, diagnosis of untreated sleep apnea, alcohol or drug abuse, and major untreated or unstable medical or psychiatric condition.

The median age of participants was 58 years, two males and three females, with median education level of general secondary education. Two participants were working during the study, one was in a reintegration process and two were not working due to their medical condition. Median time since stroke was 12 years and median insomnia duration was 9 years, all participants were in chronic stage following stroke. Three participants were evaluated with home oximetry and/or poly(somno)graphy and had no sleep apnea, in the other two participants a formal diagnostic was missing. All participants suffered from pain, psychiatric complaints, or cognitive impairments. See Table 2.

Procedure and context

Potential participants were identified by their psychologist at their first visit to an outpatient brain injury team at a rehabilitation centre in The Netherlands. After providing information and signing informed consent, an assessment was planned to check eligibility. The assessment was carried out by a research assistant and involved a structured interview following DSM-5 criteria for insomnia

Table 1. Overview of measurement

| Participant | Primary outcome: Sleep diary | | | | | Secondary outcome measures | | |
|-------------|--------------------------------|---|-------------------------------|---------------|--------------------|----------------------------|--------|-----------|
| | Daily measurements for 70 days | | | – | Follow up | Pre | Post | Follow up |
| 1 | Baseline (15 days) | Intervention phase of 6 weeks (42 days) | Posttreatment phase (13 days) | 6 week period | Follow up (7 days) | Week 1 | Week 9 | Week 16 |
| 2 | Base-line (7 days) | Intervention phase of 6 weeks (42 days) | Posttreatment phase (21 days) | 6 week period | Follow up (7 days) | Week 1 | Week 7 | Week 16 |
| 3 | Baseline (21 days) | Intervention phase of 6 weeks (42 days) | Post-treatment (7 days) | 6 week period | Follow up (7 days) | Week 1 | Week 9 | Missing |
| 4 | Baseline (14 days) | Intervention phase of 8 weeks, 6 days (62 days) | | 6 week period | Follow up (7 days) | Week 1 | Week 9 | Week 16 |
| 5 | Base-line (9 days) | Intervention phase of 6 weeks (42 days) | Posttreatment (19 days) | 6 week period | Follow up (7 days) | Week 1 | Week 8 | Week 16 |

Table 2. Demographic characteristics and relevant clinical features*

| Participant | Age (sex) | Education | Time since stroke | Stroke hemisphere | Insomnia duration | Sleep apnea | Sleep relevant medication | Pain | Psychiatric complaints | Cognitive impairments | Working |
|-------------|-----------|-----------|-------------------|-------------------------|-------------------|-------------|--|------|------------------------|-----------------------|------------------------------------|
| 1 | 65 (F) | 5 | 12 years | Right | Unclear | No | No | No | Anxiety | No | Yes |
| 2 | 48 (M) | 4 | 2 years | Right | 2 years | No | No | Yes | Mood | Yes | Start of vocational rehabilitation |
| 3 | 58 (F) | 6 | 21 years | Right | 9 years | No # | Yes; oxazepam | Yes | Mood | Yes | No |
| 4 | 31 (M) | 5 | 1 year | Subarachnoid hemorrhage | 1 year | No # | Yes; valproate methylphenidate marihuana | Yes | Mood, ADHD | No | Yes |
| 5 | 59 (F) | 5 | 25 years | Brainstem | > 20 years | No | Yes; oxazepam | No | Mood | Yes | No |

*Verhage coding of education levels (5 = average education level).

#No formal diagnosis of sleep apnea has been performed.

disorder, and an examination of medical and psychiatric history. Following assessment, participants started a daily registration in a sleep-diary app, which functioned as a baseline for the sleep measurements. The intervention phase was randomized to start between day 8 and day 21 of the study period. The secondary outcome measures, including neuropsychological tests and questionnaires, were administered face-to-face by the research assistant at baseline, posttreatment and follow up (see Table 1). All face-to-face contacts took place in a therapy room at the rehabilitation centre

The therapy room contained a table with two chairs and a working desk, in a stimulus poor environment. Participants continued daily sleep diary registration throughout all phases. Participants continued usual care during the study, this was not aimed at sleep or fatigue. Users of sleep medication were encouraged to finish medication before enrolment or to keep intake stable during the study period. No monetary rewards were provided in this study.

Approval

The study was approved by the ethical board of the research department at Heliomare Rehabilitation.

Measures

Sleep diary

A sleep diary application (available on mobile phone and desktop), based on the consensus sleep diary (Carney et al., 2012), was used daily to register total sleep time (TST), sleep onset latency (SOL), number of nocturnal awakenings (NA), sleep efficiency (SE), and sleep quality (SQ). Sleep quality was rated on a five-point scale (0 = very bad to 4 = very good). A reminder to fill in the diary was automatically sent each morning at a time which suited the participant.

Insomnia severity

The Insomnia Severity Index (ISI) is a widely used measure to index changes in insomnia severity (Morin et al., 2011). The total score ranges from 0 (no insomnia) to 28 (severe insomnia). A cutoff of 10 is used to indicate clinical levels of insomnia, similar to other studies (Lancee, Eisma, van Straten & Kamphuis, 2015; Lancee, Van Straten, Morina, Kaldo & Kamphuis, 2016; Morin et al., 2011). The Minimal Clinically Important Difference (MCID) is a reduction of six points (Yang, Morin, Schaefer & Wallenstein, 2009). The internal consistency is adequate (Cronbach's $\alpha = 0.740.78$). The ISI is selected as it is sensitive to treatment response (Bastien, Vallières & Morin, 2001; Morin et al., 2011), validated for a comparable population with traumatic brain injury (Kaufmann et al., 2017), and used in comparable research worldwide.

Fatigue, emotion, cognition and societal participation

Fatigue severity was measured with the Checklist Individual Strength – subscale fatigue (CIS-f). CIS-f has good reliability and is validated for the stroke population (Zedlitz, Van Mierlo, Van Eijk, Geurts & Fasotti, 2016). In patients with poststroke fatigue, a cutoff of >40 is regarded as severely fatigued, and MCID = -8 (Zedlitz, Rietveld, Geurts & Fasotti, 2012).

Anxiety and depression symptoms were assessed with the Dutch version of the 14-item Hospital Anxiety and Depression Scale (HADS). The internal consistency is good (Cronbach's $\alpha = 0.71-0.90$) as is the test-retest reliability (0.86–0.90) (Spinoven et al., 1997). A cutoff of >19 using total score is used to indicate clinical depression or anxiety, with sensitivity of 49%, and specificity of 96% (Spinoven et al., 1997).

Several cognitive functions, including working memory, episodic memory, attention, information processing, and aspects of executive functioning have been shown to be affected in people

with insomnia (Fortier-Brochu, Beaulieu-Bonneau, Ivers & Morin, 2012). Working memory was tested with letter number sequencing (test–retest reliability $r = 0.78$) (Wechsler, 2012), episodic memory with the Dutch parallel versions of Rey auditory verbal learning test (test–retest reliability immediate recall $r = 0.69$; delayed recall $r = 0.67$) (Schmidt, 1996; Van der Elst, Van Boxtel, Van Breukelen & Jolles, 2008), attention with the d2 test (test–retest reliability $r = 0.88$) (Brickenkamp & Zillmer, 2010), information processing with digit symbol substitution test (test–retest reliability $r = 0.87$) (Wechsler, 2012) and executive functioning with the Tower of London (test–retest reliability move score $r = 0.45$) (Lemay, Bédard, Rouleau & Tremblay, 2004; Shallice, 1982). The Cognitive Failure Questionnaire (CFQ) is a measure of subjective impression of failures in cognition. Internal consistency is good (Cronbach's alpha = 0.88) as is the test–retest reliability of 0.83 (Ponds, Van Boxtel & Jolles, 2006). A cutoff of >43 indicates more than average cognitive failures.

The Utrecht Scale for Evaluation of Rehabilitation – Participation (USER-Participation) is a questionnaire rating objective and subjective participation after rehabilitation, and is validated in an outpatient rehabilitation population with mild cognitive and physical limitations, including patients with brain injury (Post *et al.*, 2012). Internal consistency is satisfactory (Cronbach's alpha = 0.70–0.91) (Post *et al.*, 2012). Test–retest reliability is 0.65 for the frequency scale, 0.85 for the restrictions scale, and 0.84 for the satisfaction scale (Van der Zee *et al.*, 2010).

Intervention

The blended eCBT-I is based on well-established CBT-I (Trauer, Qian, Doyle, Rajaratnam & Cunnington, 2015; Zachariae *et al.*, 2016), and includes sleep hygiene education, stimulus control, sleep restriction, cognitive restructuring, relaxation, fatigue, and stress management. The eCBT-I has been adjusted to people with acquired brain injury and includes specific education about the nature and treatment of insomnia after brain injury (Ouellet, Beaulieu-Bonneau, Savard & Morin 2019). The eCBT-I comprises six guided weekly sessions, which are provided completely online, combined with two face-to-face sessions. Each online session contains specific information around one topic, assignments, and testimonials of two patients with insomnia after brain injury to illustrate sleep problems. First face-to-face session was at the beginning of the intervention phase, to make sure that the participants understood the online tool and would start motivated. Second face-to-face session was planned two weeks later, to stimulate adherence to the intervention and diary app. All sessions lasted approximately 60 min for the participant. The healthcare psychologist supported implementation of the intervention, reinforced intended steps, and provided suggestions for specific sleep interventions, such as sleep restriction (based on the sleep diary). Participants received written online personal feedback on the sleep diary registration and the online sessions, and were encouraged to practice daily with the provided exercises. Providing feedback takes approximately 15 min per session for the therapist. A therapist guide for the written feedback on each online session is included in the online intervention. See Table 3 for an overview of all sessions and main feedback tips for the psychologist. The completion time of the intervention, the adherence to the online sleep diary app, and whether participants completed all sessions and online assignments were all recorded.

Data analysis

Primary analysis was aimed at sleep diary data, using visual and statistical analysis. First, all sleep diary outcomes for each participant were presented graphically to allow for structural visual analysis of baseline, intervention, posttreatment phase, and follow-up based on the protocol of Kratochwill (Kratochwill *et al.*, 2013). The following six features of the data patterns within and between phases were visually assessed: the overall phase mean (level), trend, internight variability, immediacy of effect, overlap between phases, and consistency of patterns across phases. See

Table 3. Overview of online cognitive behavioral therapy for insomnia (eCBT-I)

| | |
|---------|--|
| Week 1: | <p>Face to face session 1: to provide information about the eHealth treatment, to plan online treatment at home (When? Where? How?), and to optimize motivation for treatment. Start of online session 1:</p> <ul style="list-style-type: none"> • Psychoeducation on sleep, the different stages (video) and sleep disorders following acquired brain injury and their consequences in daily life. Explanation of vicious circle of disrupted sleep and maintaining factors. Common comorbid factors such as pain, fatigue, disrupted daily routines and sleep apnea are addressed. • Homework assignment: map personal sleep problems and their consequences for daily life together with coping so far: what was helpful and what was not? • Start with a daily online sleep diary, which will be continued throughout the treatment. • Specific feedback tip for the therapist: highlight importance of sleep diary. |
| Week 2: | <p>Online session 2:</p> <ul style="list-style-type: none"> • Setting personal goals for treatment, information about sleep hygiene, including stimulus control. • Homework assignment: complete a checklist on sleep hygiene and write down sub goals to improve sleep hygiene for the following week. • Specific feedback tip for the therapist: start sleep restriction and/or stimulus control if indicated, reinforce intended steps to improve sleep hygiene and continued use of sleep registration, feedback on sleep diary. |
| Week 3: | <p>Face- to- face session 2: evaluate the personal goals for treatment, adjust unrealistic goals/expectations, review of problems encountered.</p> <p>Online session 3:</p> <ul style="list-style-type: none"> • Information on the relation between stress and sleep and different relaxation techniques. Audio exercises for relaxation (downloadable). • Homework assignment: practice of these relaxation techniques in the following week. • Specific feedback tip for the therapist: keep reinforcing behavioral modification and use of sleep diary, check sleep diary for possible stress factors influencing sleep, motivate to implement relaxation techniques. |
| Week 4: | <p>Online session 4:</p> <ul style="list-style-type: none"> • Information on the circadian clock which is entrained by light and temperature and the influence of activation on daytime sleepiness. Activity list for inspiration included. • Homework assignment: to balance activities and relaxation or to be more active during daytime. • Specific feedback tip for the therapist: keep reinforcing behavioral modification and use of sleep diary, feedback on sleep diary. |
| Week 5: | <p>Online session 5:</p> <ul style="list-style-type: none"> • Different cognitive techniques, such as mindfulness and cognitive restructuring, including exercises. • Homework assignment: address and change unhelpful cognitive beliefs, practice with exercises. • Specific feedback tip for the therapist: keep reinforcing behavioral modification and use of sleep diary, feedback on sleep diary, address unhelpful beliefs of sleep. |
| Week 6: | <p>Online session 6:</p> <ul style="list-style-type: none"> • Consolidation and relapse prevention. • Homework assignment: review of treatment goals and helpful steps, plan to prevent relapse. • Specific feedback tip for the therapist: review of progress, support plan for maintenance of treatment goals. |

the original article for a more detailed description (Kratochwill et al., 2013). Mean and standard deviation of all sleep diary data in each phase for each participant were reported. A randomization test suitable for AB- phase design derived from Dugard et al. (2012) was conducted to evaluate statistical significance of change in sleep outcomes across phases (Dugard et al., 2012). Applying a randomization test requires some aspect of the design to be randomized. Therefore, starting point of intervention was randomized between participants. For statistical reasons, the number of obtained data points should be equal for all participants, in our case 70 data points. Given that the baseline was variable between 7 and 21 days, and that the intervention phase had a fixed length, the post-treatment phase was also variable between 7 and 21 days (see Table 1). Differences between baseline phase (A) and intervention phase (B) in sleep diary data were

evaluated for each diary outcome, using a macro syntax in SPSS for multiple baseline AB design. Note that the measurements of the posttreatment phase were added to those of the intervention phase. This was done because the effect of intervention is expected to be long-lasting and thus to be maintained in the posttreatment phase. Sleep diary data of follow-up were not included in statistical analysis. The macro takes a random sample with replacement of 5000 pairs of intervention points and calculates the difference between intervention (combined intervention and posttreatment phase) and baseline means for each pair, to estimate the position of our test statistic in the reference set. The test statistic on group-level entails the sum over the participants of the difference between the intervention and baseline means. The one-tailed *p*-value is the probability of obtaining by chance a result at least as extreme as the actual data. Thus, a significant outcome implies that the obtained data are not likely to be found by chance, implying that at least one participant achieved a significant improvement. Missing data in the sleep diary were handled by replacing it with the phase mean.

In secondary analyses we explored clinical improvement at posttreatment and follow up. We considered improvement clinically successful if participants no longer fulfilled DSM-5 criteria for insomnia and scored below the ISI threshold (<10) for clinical insomnia. To identify clinically significant change for an individual participant on the questionnaires and tests at posttreatment and follow up, we used the minimal clinically important difference (MCID) for ISI, CIS-20 and USER-P, and the reliable change index (RCI) for HADS, CFQ, and neuropsychological tests (Jacobson & Truax, 1991).

Results

Completion of intervention

All five participants completed all sessions and online assignments of the eCBT-I. Face-to face sessions took place according to schedule. The intervention was completed within 6 weeks for four participants. Adherence to use the sleep diary was 88% of the days across all phases for participant 1, 2, 3 and 5 (range 77%–100%). Participant 4 completed the intervention in 8 weeks and 6 days, with a delay due to personal problems that warranted attention. He filled in 35% of the sleep diary during baseline and the beginning of the intervention, as he missed successive notifications to fill in the diary for unknown reasons halfway through. Follow-up questionnaires and tests of participant 3 were not conducted, as the participant stated that it was too stressful to complete this measurement at follow up. See Supplementary Tables 1 and 2 for missing values.

Outcomes

Sleep diary

Figures 1–5 show the sleep diary outcomes for each participant during baseline, intervention, posttreatment and follow up. Participant 4 is excluded from the diary analysis as a result of missing diary data of the posttreatment phase. See Table 4 for an overview of mean and standard deviation of sleep outcome measures for each participant in each phase. A raw data record is provided in Supplementary Table 3.

Structured visual analysis (Kratochwill *et al.*, 2013) of total sleep time showed no clear visually perceptible trend or improvement of average total sleep time between phases (Fig. 1). For participants 1, 2, and 3 internight variability decreased during intervention, with less shorter nights at the end of intervention and posttreatment phase. Internight variability increased for participant 5, contrary to expectation. A randomization test (one-tailed) to test the prediction that eCBT-I would improve total sleep time in four participants found that 44% of a random sample of 5000 rearrangements statistics was at least as large as our experimental value. This is not significant (Test statistic = 1.77; $p = 0.44$).

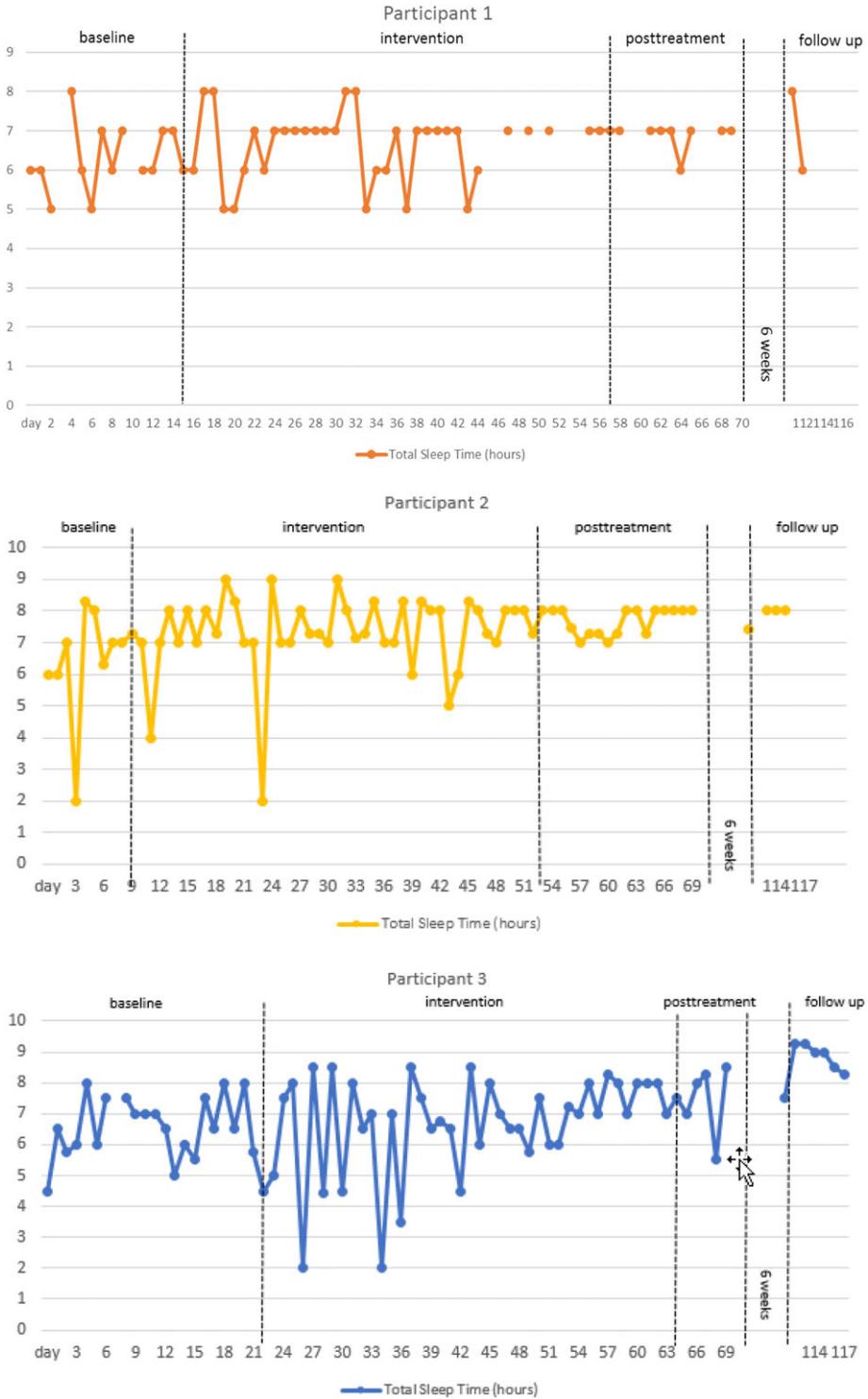


Figure 1. Daily reports of total sleep time (hours).



Figure 1. (Continued)

Visual analysis of nocturnal awakenings showed a decrease of average posttreatment for participant 1, and no clear perceptible trend or improvement for participants 2, 3, and 5 (.2). Internight variability decreased for participant 1 and 2 and increased for participant 5. A randomization test (one-tailed) to test the prediction that eCBT-I would decrease nocturnal awakenings in four participants found that 4% of a random sample of 5000 rearrangements statistics was at least as large as our experimental value. This is significant at the 5% level, implying that at least one participant achieved a significant decrease of nocturnal awakenings in the intervention phase (Test statistic = 3.20; $p = 0.04$).

Available data of sleep onset latency showed no clear visually perceptible trend or improvement (Fig 3). The randomization test (one-tailed) was performed over data of participants 3 and 5 and showed no significant improvement of sleep onset latency (test statistic = -17.36; $p = 0.75$).

Visual analysis of sleep efficiency showed no clear perceptible trend or improvement (Fig. 4). The randomization test was executed on grouped data of participants 3 and 5 and showed no significant improvement of sleep efficiency (test statistic = 3.04; $p = 0.29$).

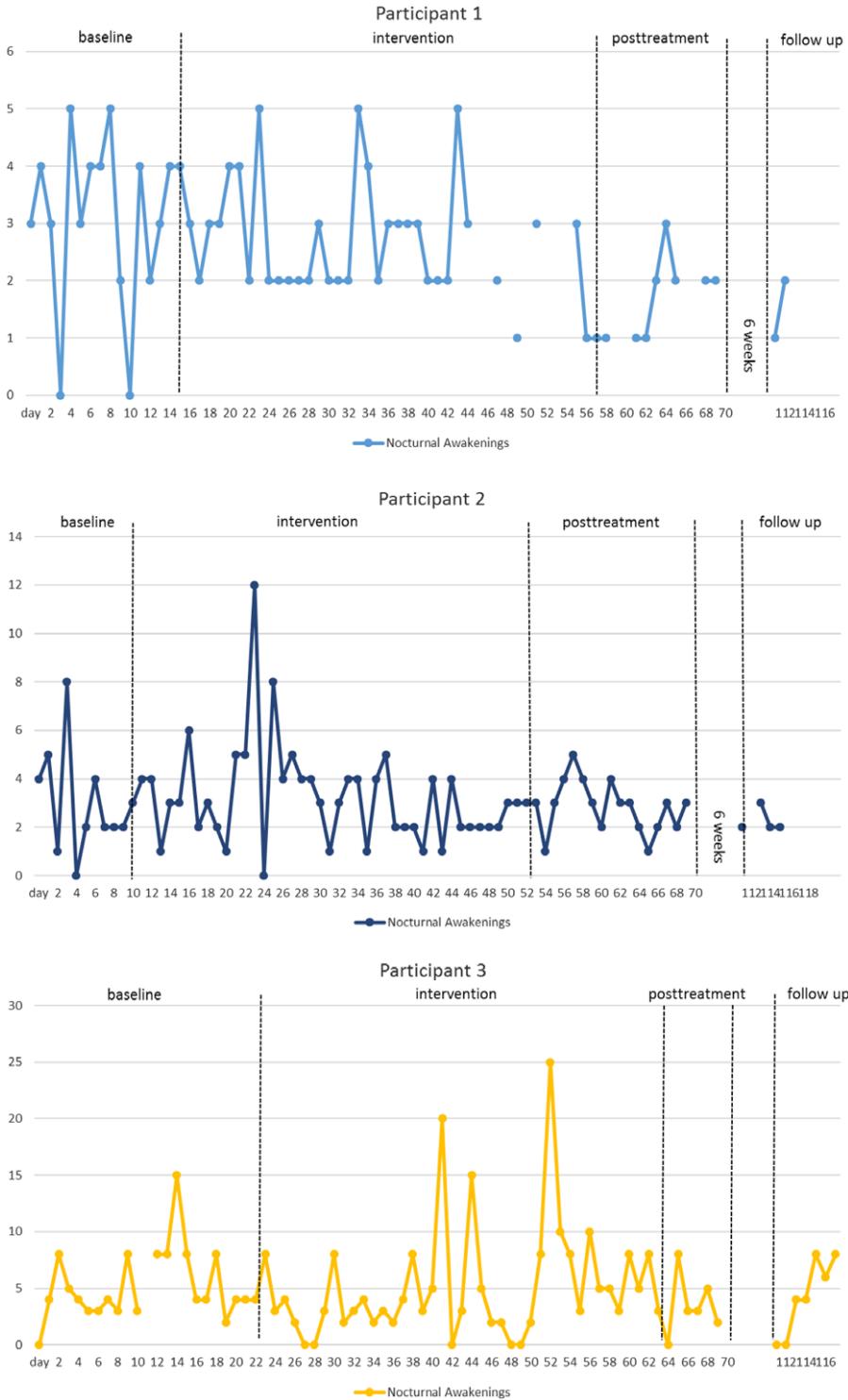


Figure 2. Daily reports of nocturnal awakenings.

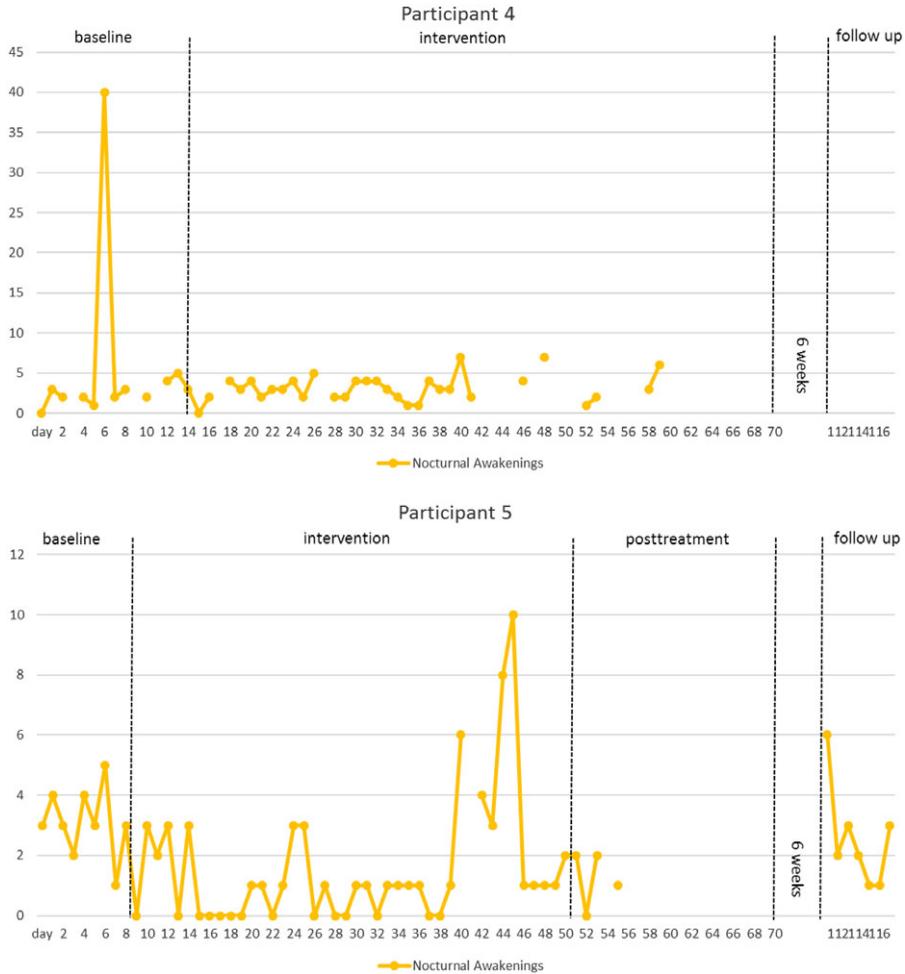


Figure 2. (Continued)

Visual analysis of sleep quality showed a positive trend and improvement of average rated sleep quality for participants 1, 2, and 3, with decreasing variability during treatment and posttreatment (Fig. 5). This was not seen for participant 5. The randomization test (one-tailed) to test the prediction that eCBT-I would improve sleep quality in four participants found that 67% of a random sample of 5000 rearrangements statistics was at least as large as our experimental value (test statistic = 1.25; $p = 0.67$).

In sum, all sleep diary measures showed a high internight variability, which is typical for insomnia. There was no immediate effect of change from baseline to intervention phase, and a high degree of overlapping data points between phases. Due to the high variance in the data and overlap it was difficult to judge the effect of intervention based on visual analysis of the diary data alone. All four participants improved on all five sleep outcome measures posttreatment or follow up (see Table 4), but improvement was small and not clearly visible, and mostly non-significant. Statistical analysis showed a significant improvement of nocturnal awakenings, but not for total sleep time, sleep onset latency, sleep efficiency, and sleep quality.

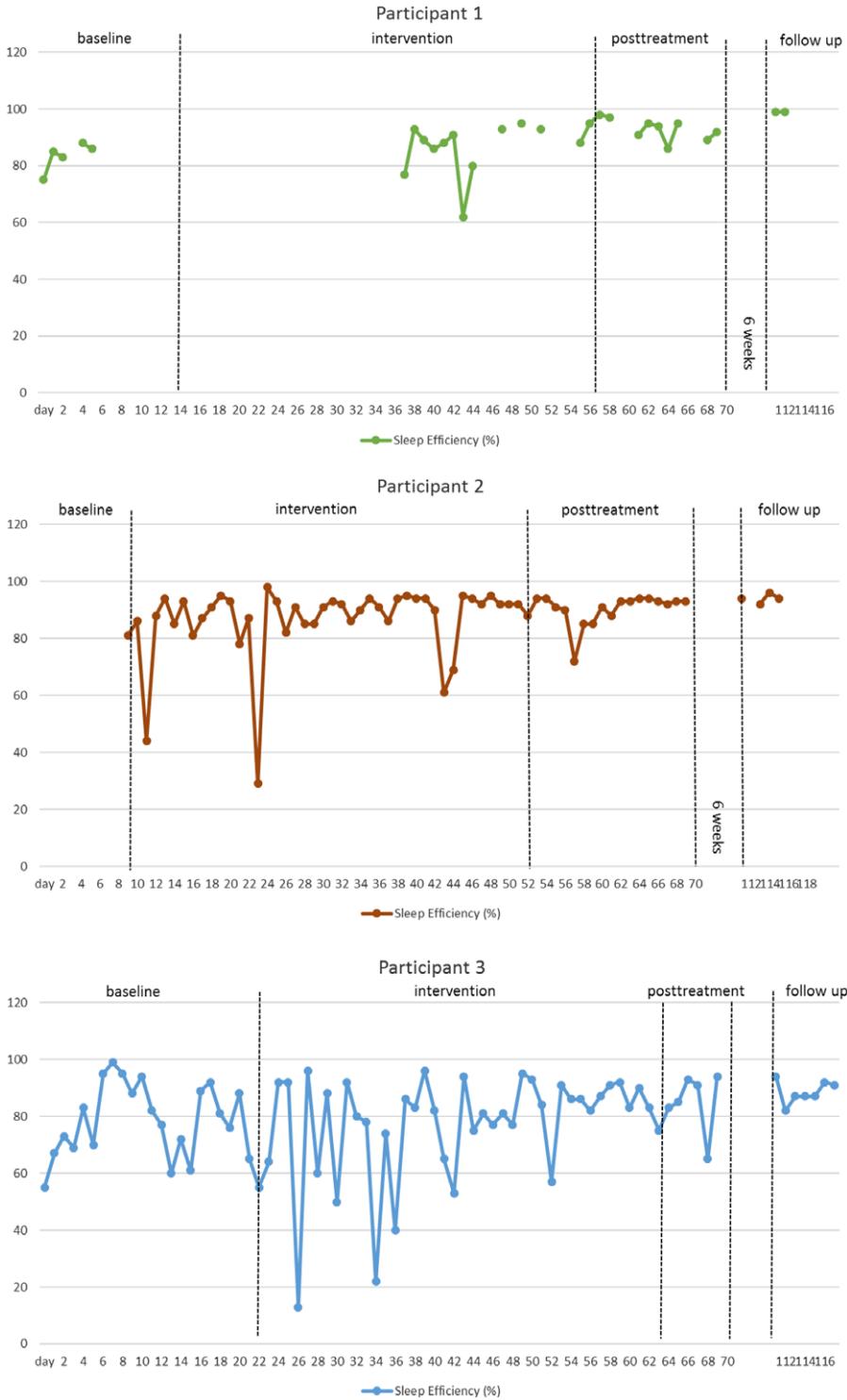


Figure 4. Daily reports of Sleep Efficiency.

Note: unreliable input due to error in diary version for participant 1 (day 7 to day 38) and participant 2 (day 1 to day 10) is reported as missing values.

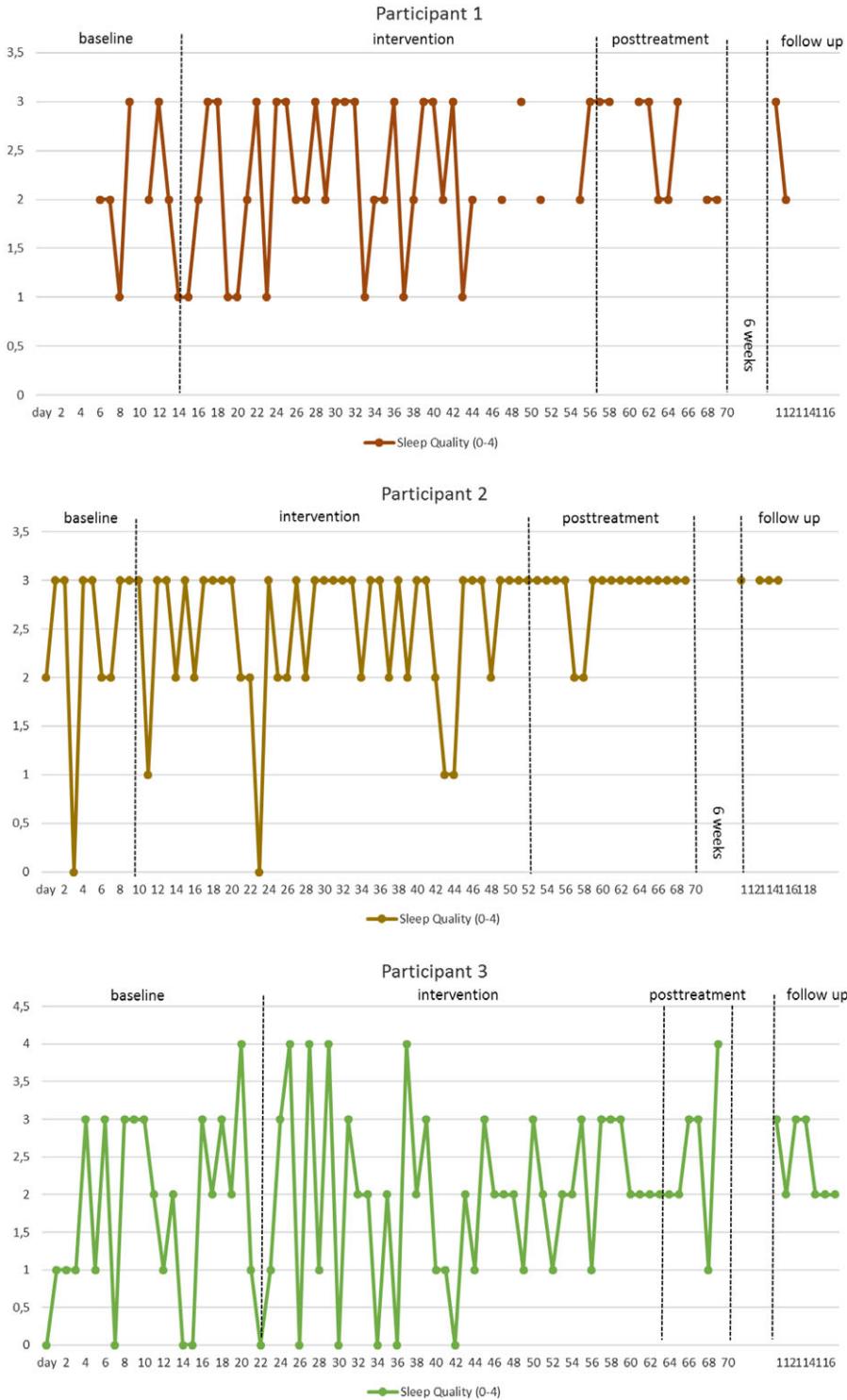


Figure 5. Daily reports of Sleep Quality (0–4). Rating of sleep quality (0= very bad to 4= very good).

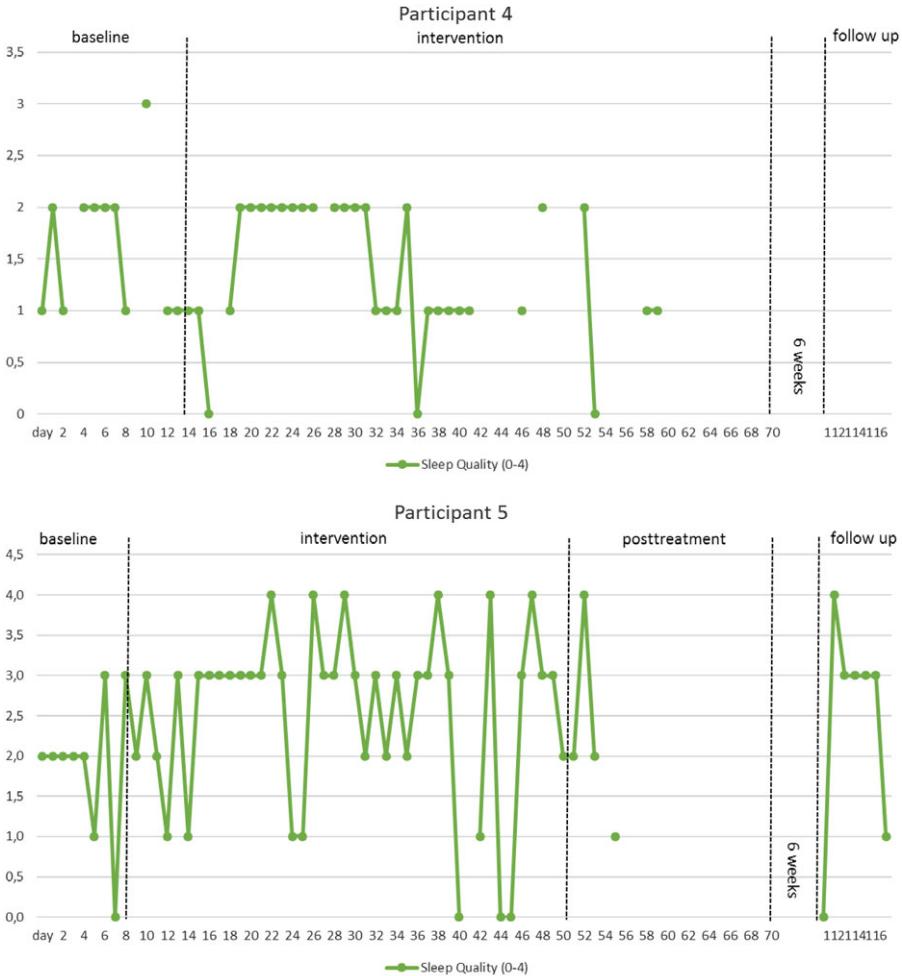


Figure 5. (Continued)

more physical complaints at the end of the treatment phase, due to an unnoticed medical condition. However, he mentioned that this did not influence his sleep. Participant 4 had personal problems during the treatment phase. Participant 5 had a fever during posttreatment measurements. Sleep relevant medication and drugs were continued in a low dose for participants 3 and 4 during the study period. Participant 5 finished medication before enrolment.

Discussion

Interpretation

This study aimed to evaluate efficacy of blended eCBT-I in five participants with post-stroke insomnia. All five completed the eCBT-I intervention and improved on insomnia severity post-treatment, as they all scored in the normal ISI range (ISI < 10) or reached a clinically meaningful improvement at posttreatment. At follow-up however, two participants reached a clinically meaningful improvement compared to baseline, while two other participants did not (data of one participant missing).

Table 4. Sleep outcome measures

| Participant | Sleep | Baseline phase | | Intervention phase | | Posttreatment phase | | Follow up (> 6 weeks) | | |
|-------------------------|-------------|----------------|------|--------------------|------------|---------------------|------------|-----------------------|------|------|
| | | Mean | SD | Mean | SD | Mean | SD | Mean | SD | |
| 1 | Sleep diary | TST (hr) | 6.3 | 0.9 | 6.6 | 0.9 | 6.9 | 0.3 | 7.0 | 1.4 |
| | | SOL (min) | 24.0 | 8.2 | 22.4 | 15.8 | 10.6 | 7.3 | 5.0 | 0.0 |
| | | NA | 3.5 | 1.0 | 2.7 | 1.0 | 1.7 | 0.7 | 1.5 | 0.7 |
| | | SE (%) | 83.4 | 5.0 | 86.9 | 9.3 | 93.0 | 3.9 | 99.0 | 0.0 |
| | | SQ | 2.0 | 0.8 | 2.2 | 0.8 | 2.6 | 0.5 | 2.5 | 0.7 |
| Insomnia Severity Index | | ISI | 18 | | 9* | | 13 | | | |
| 2 | Sleep diary | TST (hr) | 6.2 | 2.1 | 7.2 | 1.3 | 7.7 | 0.4 | 7.9 | 0.3 |
| | | SOL (min) | # | # | 41.6 | 43.0 | 20.0 | 5.9 | 13.8 | 4.8 |
| | | NA | 3.4 | 2.7 | 3.2 | 2.1 | 2.8 | 1.0 | 2.3 | 0.5 |
| | | SE (%) | # | # | 86.1 | 13.7 | 90.4 | 5.0 | 94.0 | 1.6 |
| | | SQ | 2.3 | 1.1 | 2.5 | 0.7 | 2.9 | 0.3 | 3.0 | 0.0 |
| Insomnia Severity Index | | ISI | 11 | | 7* | | 4* | | | |
| 3 | Sleep diary | TST (hr) | 6.6 | 1.0 | 6.6 | 1.6 | 7.4 | 1.0 | 8.7 | 0.6 |
| | | SOL (min) | 71.4 | 61.1 | 83.6 | 90.0 | 72.9 | 47.8 | 48.6 | 26.7 |
| | | NA | 5.3 | 3.3 | 5.2 | 5.1 | 3.4 | 2.5 | 4.3 | 3.4 |
| | | SE (%) | 79.3 | 12.8 | 76.5 | 19.2 | 83.7 | 10.6 | 88.6 | 4.0 |
| | | SQ | 1.8 | 1.2 | 1.9 | 1.2 | 2.4 | 1.0 | 2.4 | 0.5 |
| Insomnia Severity Index | | ISI | 25 | | 6* | | - | | | |
| 4 | Sleep diary | TST (hr) | 6.2 | 1.7 | 6.0 | 1.6 | - | - | - | - |
| | | SOL (min) | 51.7 | 55.9 | 53.0 | 70.3 | - | - | - | - |
| | | NA | 5.8 | 11.4 | 3.1 | 1.6 | - | - | - | - |
| | | SE (%) | 82.3 | 12.5 | 75.8 | 15.9 | - | - | - | - |
| | | SQ | 1.6 | 0.7 | 1.4 | 0.7 | - | - | - | - |
| Insomnia Severity Index | | ISI | 20 | | 12* | | 13* | | | |
| 5 | Sleep diary | TST (hr) | 5.5 | 1.1 | 5.6 | 1.4 | 5.6 | 1.2 | 5.9 | 0.9 |
| | | SOL (min) | 48 | 84 | 55 | 63 | 56 | 83 | 32 | 27 |
| | | NA | 3.1 | 1.2 | 1.6 | 2.2 | 1.3 | 1.0 | 2.6 | 1.7 |

(Continued)

Table 4. (Continued)

| Participant | Sleep | Baseline phase | | Intervention phase | | Posttreatment phase | | Follow up (> 6 weeks) | |
|-------------|-------------------------|----------------|------|--------------------|------|---------------------|------|-----------------------|------|
| | | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| | SE (%) | 76.4 | 17.7 | 81.7 | 18.7 | 78.0 | 19.9 | 80.7 | 16.8 |
| | SQ | 1.9 | 0.9 | 2.5 | 1.1 | 2.3 | 1.3 | 2.4 | 1.4 |
| | Insomnia Severity Index | ISI | 18 | | | 7* | | 15 | |

TST, total sleep time; SOL, sleep onset latency; NA, nocturnal awakenings; SE, sleep efficiency; SQ, sleep quality (0= very bad to 4= very good); ISI, insomnia severity index; hr, hours; min, minutes.

Note: # (partial) Unreliable input due to error in diary version. Missing diary input of participant 4 during posttreatment and follow up.

*Clinical improvement if ISI < 10 or MCID > 6 compared to baseline.

Four participants completed the sleep diary throughout, while one participant stopped using the diary app, while the other four completed it throughout. Significant improvement was only found for nocturnal awakenings, and not for total sleep time, sleep onset latency, sleep efficiency, and sleep quality. As sleep was not expected to improve immediately after the start of intervention, the absence of significance could be partly attributable to our conservative statistical approach of testing the difference between adjacent phases, instead of the difference between baseline phase with the end of the intervention phase. However, it should be noted that it was also difficult to judge effect of intervention based on visual analysis alone. A possible explanation of the absence of clear effects on the sleep diary data could be that the outcomes of three participants (2, 4, and 5) were adversely affected by health and personal events. As a result, the therapy benefit is not as evident from the sleep diary data as it was from perceived insomnia severity at posttreatment. Also, the intervention may not be effective for improving sleep diary measures in its current format. More emphasis on sleep restriction may enhance effectiveness on sleep efficiency, for example. It must be noted that the sleep diary and the ISI measure different aspects of sleep. The sleep diary assesses the perceived length of nocturnal symptoms, while the ISI focuses more on perceived severity, including effects of poor sleep on daytime functioning. Differential treatment effects, depending on the outcome measure, are also found in the general population, with larger effect sizes of eCBT-I for insomnia severity (Hedges's g 0.98–1.09) than for the sleep diary data (Hedges's g 0.29–0.71) (Van Straten *et al.*, 2018). Another possible explanation for the absence of clear improvement is that individuals with a stroke may need a longer period to implement sleep promoting strategies due to cognitive deficits. Compared to the other CBT-I studies in brain injury populations, the treatment duration in our study is short (Herron *et al.*, 2018; Nguyen, McKay, *et al.*, 2017; Nguyen, Wong, *et al.*, 2017; Ouellet & Morin, 2007). Longer treatment duration might be associated with larger effects (Zachariae *et al.*, 2016).

After completion of the treatment, four out of five participants no longer fulfilled DSM-5 criteria for insomnia disorder and scored in the normal ISI range (<10). As all participants were in chronic stage following stroke, changes due to spontaneous recovery are unlikely. Cognitive deficits, psychiatric comorbidity or pain of the participants were no barrier to adhere and benefit from eCBT-I. Exploratory analyses revealed slight improvements on subjective measures of fatigue, emotional well-being and cognitive functioning, and all participants exhibited reliable change on at least one neuropsychological test posttreatment. It should be emphasized that the statistical importance of this finding is minimal, given the number of outcome measures and the limitations of RCI calculation. For RCI calculation the test-retest reliability is used when available, however the test-retest reliability of the neuropsychological tests is often based on longer

test interval between measurements than the interval of 6 weeks in our study. Although we used a parallel version of the Rey auditory verbal learning test, potential learning effects could not be totally excluded.

These outcomes are in line with the outcomes of face-to-face CBT-I in stroke studies (Herron et al., 2018; Nguyen, Wong, et al., 2017) and eCBT-I in a population with traumatic brain injury (Theadom et al., 2017). Comparable efficacy of both face-to-face CBT-I and eCBT-I is also found in the general population (Seyffert et al., 2016).

Strengths and Limitations

All five potential participants with post-stroke insomnia agreed to participate to the intervention. The participants in our study had comparable or more severe psychiatric complaints than the participants with post-stroke insomnia in other CBT-I studies (Herron et al., 2018; Nguyen, Wong, et al., 2017), in addition to pain and cognitive impairments also reported. The time since stroke and insomnia duration is long in our participants. For the general population insomnia duration is associated with larger treatment effect (Zachariae et al., 2016). Larger group studies are needed to clarify the moderators of efficacy of eCBT-I in a stroke population. Another strength is the high completion rate, even more so if compared to the drop-out rate of 24.7% found in a meta-analysis of efficacy of eCBT-I in the general population (Zachariae et al., 2016). A methodological strength of the single case experimental design is the high level of internal validity. However, some limitations should be noted. First, participants were inevitably not blinded, so treatment expectations could have influenced the outcome. Findings might be partly attributable to other interventions, as eCBT-I was added to treatment as usual, or to the passage of time. However, this seems unlikely, as other interventions were not aimed at sleep and no improvement during baseline was seen, while treatment as usual already had started. Second, there is a potential bias due to missing data. Sleep diary data of participant 4 and follow up questionnaires of participant 3 are missing. Compared to baseline both participants improved on other sleep outcome measures, and therefore seemed to benefit from intervention. Third, we used a conservative approach to analyze the SCED data that might have influenced significance of results, and lead to a type II error. The advantages of this method are that it is non-parametric and allows combining data of several participants in the multiple baseline AB-design. However, there is no consensus of which method of statistical analysis is most appropriate for SCED data, and different analytical techniques could lead to different conclusions (Evans, Gast, Perdices & Manolov, 2014). Nonetheless, as visual analysis also showed no large improvements on diary data, this seems not likely in this study. Even so, only subjective sleep outcome measures were included. Fourth, two of our participants reclined at follow up. This might be partly attributable to a fever of one of participant during that period. Another possibility is that people with acquired brain injury need more encouragement or reminders due to cognitive problems to stay adherent to the intervention in order to prevent relapse. And finally, the design and small sample size limits generalizability of the results to a larger population with post-stroke insomnia. Generalizability to an older age group is particularly limited, as participants in this study were relatively young stroke survivors. Since the large self-directive component of eCBT-I may be challenging for some patients, it would be useful to determine which personal factors predict the success of this type of intervention. Future research should further extend to a randomized controlled trial with a large sample, using both subjective and objective (e.g., actigraphy) outcome measures of sleep at posttreatment and follow up to draw stronger conclusions on the efficacy of eCBT-I for post-stroke insomnia.

Conclusion

Blended eCBT-I might be an effective treatment option for patients with poststroke insomnia, but also needs further investigation, in particular in regard to long-term efficacy. This study provides

justification for a randomized clinical trial. If effective, offering the intervention online may facilitate its dissemination to therapists and patients.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Data availability statement. The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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