의학석사 학위논문

수면지표기반 불면증 디지털 치료기의 효과와 안전성: 무작위, 이중 맹검 전향적 연구

Effectiveness and Safety of Digital Therapeutic Application of Sleep-Index Based Treatment for Insomnia (dSIBT-I): A Randomized Double-blind Prospective Study

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2023 년 8 월

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Abstract

Introduction

This study aimed to evaluate the effectiveness and safety of the digital Sleep-Index Based Treatment for Insomnia (dSIBT-I) for patients with insomnia and compare it with those of the digital Cognitive Behavioral Therapy for Insomnia (dCBT-I).

Methods

This randomized prospective study was conducted at Asan Medical Center. Fifty patients with insomnia were recruited between December 2022 and January 2023 and randomly assigned to the dSIBT-I group or the dCBT-I group. Outcomes were assessed weekly for a 1-month period. The primary outcome was Insomnia Severity Index (ISI) score at Week 4, whereas the secondary outcome was the proportion of participants whose ISI scores were less than 15 at Week 4. We conducted linear mixed model and generalized estimating equation analyses.

Results

Both the dSIBT-I group and the dCBT-I group showed significant improvements in ISI scores during the therapy. There was no significant difference between the two groups in terms of ISI scores at Week 4 and the proportion of participants whose ISI scores were reduced to less than 15 at Week 4. However, at Week 2, the dSIBT-I group showed better results than the dCBT-I group in the two outcomes. No treatment-emergent adverse events were reported in both groups.

Conclusion

The dSIBT-I is as safe and effective as the dCBT-I for patients with insomnia with more rapid treatment effects.

Key words: sleep, insomnia, digital technology, cognitive behavior therapy, software

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Introduction

With the development of neuroscience and psychiatry, there have been many efforts to improve patients' sleep. Quality of life is highly influenced by how well people sleep, and although sleep difficulties may occur occasionally owing to environmental changes or stressful events, it becomes serious if it occurs too frequently. Insomnia refers to difficulty sleeping, and this term is used in various contexts with different definitions. For instance, it is frequently used to describe patients' subjective difficulties with falling asleep or maintaining sleep. In other cases, it explains the abnormalities in patients' polysomnography. However, insomnia disorder is a specific diagnosis, which is characterized as a consistent dissatisfaction with the quantity or quality of sleep, causing significant distress in an individual's everyday life.

Numerous studies have examined the prevalence of insomnia. Overall, the prevalence of insomnia in the general population is assumed to be between 10% to 40%[1]. The results differ according to several factors, such as whether insomnia was defined as a symptom or disorder and the region in which the study was conducted. According to a multicenter cross-sectional study which included 57,298 participants from 66 different sites, 11.2% of all participants were diagnosed with acute insomnia, with the prevalence ranging widely from 2.3% in Tonga to 25.5% in Alger[2]. In South Korea, a population study with 3719 participants concluded that 17% of the sample suffered from insomnia symptoms occurring at least 3 nights per week, and 5% of the sample fulfilled the diagnostic criteria of DSM-IV insomnia disorder[3]. Another population-based cohort study in South Korea showed that the standardized prevalence of insomnia based on ICD-10 diagnosis or prescription of sedatives increased from 3.1% to 7.2% in women and 1.62% to 4.32% in men from 2002 to 2013[4].

Insomnia has several negative effects on both the individual and society. Insomnia is associated with an individual's mental and physical health. The correlation between insomnia and other

psychopathologies, such as depression and anxiety, has been shown in numerous studies. Although insomnia can be a consequence of another primary psychiatric disorder, it can also precipitate to or aggravate other psychiatric disorders. According to a meta-analysis of 21 longitudinal studies, the risk of depression was double in people with insomnia compared with those who had no sleep difficulties[5]. Furthermore, a systematic review and meta-analysis of five prospective cohort studies concluded that insomnia was a significant risk factor for dementia[6]. Insomnia is also associated with impaired daytime functioning[7]. Moreover, the social consequences of insomnia cannot be neglected. Previous research proves that insomnia is either directly or indirectly linked with various societal costs. For instance, according to a case-control study of American Medicare beneficiaries, those with untreated insomnia had higher health care utilization rates and economic costs owing to factors, such as increased admission and frequent emergency department visits[8]. A cross-sectional study of a US company's employees showed that insomnia led to higher presenteeism and decreased work productivity[9]. A population-based survey study conducted in Italy showed that middle-aged drivers with insomnia were approximately three times more likely to experience road accidents[10]. As such, developing an efficient treatment for insomnia is of utmost importance in modern society.

Cognitive Behavior Therapy for Insomnia (CBT-I)

Cognitive behavior therapy for insomnia (CBT-I) refers to a non-pharmacological multi-component treatment of insomnia based on behavioral principles and cognitive restructuring[11]. Owing to the growing evidence of its high long-term efficacy and low possibility of side-effects, many guidelines recommend this non-pharmacological approach as an initial treatment for chronic insomnia[12]. Conventional CBT-I consists of individual sessions dealing with sleep hygiene, stimulus control, sleep restriction, cognitive therapy, and relaxation training[13]. Each session is delivered on a weekly or "alternate week" basis; thus, the total intervention takes 4-8 weeks. Among the components, stimulus

control is best-established with research and evidence and is therefore used as a first-line behavioral therapy[14]. It consists of instructions to prevent patients from spending time in the bed or bedroom doing things other than sleeping. For instance, patients are instructed to go out of the bedroom and move to another place if they do not feel drowsy. Sleep restriction is an intervention to delay the patients' bedtime to adjust the time in bed (TIB) to approximate total sleep time (TST). This results in decreased sleep latency as well as increased sleep efficiency. Sleep hygiene education addresses behaviors that interfere with sleep quantity or quality. Typically, patients are given a handout that contains several instructions, such as exercising regularly, eating regular meals, and avoiding alcohol. Cognitive therapy aims to alleviate patients' anxiety or arousal by correcting their false or exaggerated beliefs about sleep (e.g., thinking that insomnia will have devastating consequences). Relaxation training includes techniques such as progressive muscle relaxation and diaphragmatic breathing.

Recently, short and long-term effects of CBT-I have been investigated and its effects have been compared with those of pharmacotherapy. According to several meta-analyses and systematic reviews, CBT-I is effective in the treatment and relapse prevention of primary insomnia[15-19]. Other studies have demonstrated that CBT-I is helpful for patients with insomnia comorbid with psychiatric and medical conditions[20-22]. Additionally, the treatment effect of CBT-I outweighs that of pharmacotherapy[23,24]. Specifically, a meta-analysis of 21 studies comparing behavioral therapy and pharmacotherapy concluded that the former led to a better reduction in sleep latency[23]. A randomized clinical trial of patients aged 25-64 years with chronic sleep onset insomnia showed that CBT-I was superior to pharmacotherapy in terms of improvements in sleep-onset latency and sleep efficiency, the proportion of patients returning to normal sleep, and long-term sustainability of therapeutic benefits[24]. Furthermore, recent studies have shown that the outcomes of CBT-I are not limited to alleviations of insomnia. According to a systematic review of 18 studies, the therapeutic effects of CBT-I on depression comorbid with insomnia are significant, and improvements in

insomnia symptoms mediate these effects[25]. A recent meta-analysis supports this result and suggests that internet-based CBT-I can improve comorbid anxiety[26]. Although further research is needed to clarify the exact mechanisms, a study showed that CBT-I helped reduce suicidal ideation among US veterans with insomnia[27]. A randomized controlled trial of 1711 patients with insomnia treated with digital CBT-I showed that it was helpful in enhancing secondary outcomes such as functional health, sleep-related quality of life, and psychological well-being[28].

There are both pros and cons of using CBT-I for the treatment of insomnia, especially compared with pharmacotherapy. One important advantage of CBT-I is that it does not have the various adverse effects of pharmacotherapy. Hypnotics, such as benzodiazepine agonists or zolpidem, are prone to cause excessive sedation, dizziness, or falls, and may impede daily functioning, especially in older adults. This can also lead to poor treatment compliance. As CBT-I is not associated with these side effects, it is considered better in terms of safety and long-term compliance. Another advantage of CBT-I is that it can be applied to patients with medical comorbidities, although treatment results may vary. For instance, patients with pulmonary disorders, such as chronic obstructive pulmonary disease, may find it difficult to use pharmacotherapy due to the potential adverse respiratory events. In such conditions, CBT-I may be the only possible treatment choice. However, one drawback of applying CBT-I is the risk of dropout. Since the complete intervention takes 4-8 weeks, some patients may not complete the entire course. Although results vary according to the type of study conducted or mode of treatment delivery, dropout rates are estimated to range from approximately 13% to as high as 57%[15,29-31]. According to a meta-analysis of 11 randomized controlled trials with 1460 participants, a larger dropout during intervention was found to lead to smaller effect sizes[32]. Another aspect to consider when discussing CBT-I is its relatively low availability. Despite guidelines supporting CBT-I as the main treatment for insomnia, the actual proportion of patients with insomnia who receive this therapy is far lower than those who take sleeping pills. A study conducted on the status of CBT-I administration in 12 European countries in 2018 showed that CBT-I was not readily

available to most patients with insomnia[33]. Various factors may contribute to this low accessibility, such as the lack of standardized training courses for therapists and longer duration of treatment, leading to the preference of clinicians for pharmacotherapy.

To enhance the availability of CBT-I in clinical practice, different modes of treatment delivery have been developed. The conventional individual face-to-face setting requires patients to visit the clinic once a week or every other week and meet the therapist for approximately 60-90 min depending on the session, which can be somewhat inefficient. A reasonable alternative to enhance the efficiency is group-based therapy, in which a group typically composed of 8-15 patients receive the treatment sessions together[34]. Another way is to deliver the treatment course through telehealth, in which the psychoeducation and treatment guidelines are the same as in conventional face-to-face CBT-I; however, in the former, the treatment course is provided through online tools, phone, or e-mail. Recent research indicates that telehealth delivery is non-inferior to face-to-face delivery in terms of insomnia treatment[35,36]. Given the advancement in new technologies, this type of CBT-I is being widely investigated.

Current status of digital therapeutic applications in healthcare

Digital therapeutics are software programs developed to prevent disease and improve treatment. They are provided to patients through mobile devices, including tablets and smartphones. The main goal of digital therapeutics is to gain therapeutic effects by helping individual patients modify their lifestyles. With increasing research on its treatment effects, its usage in various medical fields is continually expanding. According to a 3-month cohort study of 118 patients with type 2 diabetes, FareWell, a novel digital therapeutic, was found to decrease HbA1c by 0.8% on average, which was clinically significant. Moreover, HbA1c was significantly reduced in participants with the highest tertile of engagement than in those with the lowest tertile[37]. Digital therapeutics have been proven

to be effective in reducing hypertension[38,39]. They can enhance adherence to medications for patients with coronary heart disease[40] or cancer[41] as a self-managed digital application.

In the last decade, digital therapeutics have been increasingly used in psychiatry. Lifestyle modification and good treatment compliance, which can be achieved more efficiently with the help of digital therapeutics, are especially important in the management of mental illness. Furthermore, CBT is the mainstay of treatment for various psychiatric disorders, and incorporating it into digital therapeutics can be more advantageous than the conventional face-to-face method. Patients' real-time conditions can be tracked thoroughly and tailored treatment strategies can be provided. In addition, digital therapeutics are cost-effective in that they do not require patients to visit the clinic every time. Therefore, research is being conducted on the application of digital therapeutics to patients with psychiatric disorders, such as major depressive disorder, panic disorder, attention-deficit/hyperactivity disorder, substance abuse disorder, and insomnia disorder[42], with several studies showing positive results. For example, an observational study evaluating 602 patients with substance use disorder treated with an Food and Drug Administration (FDA)-authorized digital therapeutic yielded an abstinence rate of 62% after 9-12 weeks of therapy[43]. Another study of 25 children diagnosed with attention-deficit/hyperactivity disorder showed that digital therapeutics targeting a specific neural marker of attention are effective in improving both attention and clinically observed symptoms of the disorder[44]. According to a randomized controlled trial of 65 patients with generalized anxiety disorder, the reduction rate in anxiety measured by Generalized Anxiety Disorder-7 scales was significantly higher in those who were treated with a digital app-delivered mindfulness training than those who received as-usual treatment[45].

Digital therapeutics are also widely studied in the management of insomnia, especially in Europe and the US. Sleepio, a digital therapeutic for insomnia developed by a company named Big Health, was used by over 12 million people in England and the US in 2019[46]. Numerous clinical trials proved the

effects of the product for improving sleep. For example, a randomized clinical trial of 1711 participants allocated to either Sleepio therapy or sleep hygiene education, both applied in addition to any treatment started before study initiation, revealed that the digital therapeutic was superior in enhancing functional health, psychological well-being, and quality of life related to sleep[28]. In 2022, Sleepio was approved by the National Institute for Health and Care Excellence as a reasonable alternative to medication for the treatment of insomnia in primary care[47]. Another digital therapeutic for chronic insomnia is Somryst, developed by an American company—Pear Therapeutics. Notably, it was the first digital therapeutic for insomnia to be cleared by the FDA[48]. A recent systematic review and meta-analysis compared the effectiveness of Somryst with conventional CBT and sleep medications; it concluded that Somryst was the most effective in terms of reducing the insomnia severity index[49]. Furthermore, other digital therapeutics for insomnia, such as BetterNight Insomnia and Night Owl-Sleep Coach, are currently available but not yet approved by authorities[50].

As such, novel digital therapeutics for insomnia are being developed and introduced. However, one problem with those available is that patients may feel bored and thus leave the treatment course incomplete. Although treatment compliance is indeed enhanced, in that patients do not need to visit the hospital frequently, there is no difference in the specific contents of CBT. If some items could be added to ensure delivery through digital means, patients might become more adherent.

The concept of Sleep-Index Based Treatment of Insomnia (SIBT-I)

CBT-I is an effective treatment for managing insomnia. However, it may have some limitations for patients, such as time and location constraints. Additionally, therapists must receive specialized training in CBT-I to provide treatment. To address these limitations, an alternative technique called Sleep Indices-Based Therapy for Insomnia (SIBT-I) has been developed. SIBT-I applies sleep patterns obtained from clinical practice to guide the proper sleep-wake cycle. It has four concepts: 1) 17 hours

of activity and 7 hours of sleep, 2) discrepancy between desired time in bed and desired total sleep time, 3) time in bed during 24 hours, and 4) taking sleeping pills 7 hours before the waking-up time[51].

Table 1. Four components of Sleep-Index based Treatment for Insomnia

Components	설명
1) 17 hours of activity and 7 hours of sleep	It is based on the concept that getting adequate activity during the day will help you sleep well at night. It is in accordance with the result that the greater the time between waking up and falling asleep, the shorter the time between bedtime and sleep onset time.
2) Discrepancy between desired time in bed and desired total sleep time	It is a treatment based on cognitive therapy, which aims to reduce the difference between the desired total sleep time and desired time in bed.
3) Time in bed during 24 hours	It has been suggested that total time in bed during 24 hours (TIB/d) has a significant correlation with sleep latency and can reflect daytime activity.
4) Taking sleeping pills 7 hours before waking-up time	It is based on evidence that taking sleeping pills 7 hours before waking up increases satisfaction.

1) Component #1 - 17 hours of activity and 7 hours of sleep

This is one of the core components of SIBT-I, which is based on the assumption that a delayed bedtime induces shorter sleep onset latency (SOL) when a fixed wake-up time is established[52]. People with insomnia want to go to bed early to fall asleep quickly. However, they cannot easily fall asleep without an adequate circadian rhythm and homeostatic pressure to promote sleep. Based on two process models of sleep regulation[53], sleep may be regulated by process S (homeostatic drive) and process C (circadian process). The longer the period of arousal, the more the pressure to sleep (process S). Additionally, sleep is regulated by a circadian rhythm, which is controlled by the suprachiasmatic

nucleus (process C). In other words, in addition to the circadian rhythm, the homeostatic drive and the pressure to sleep are required to ensure adequate sleep. In a previous study, short SOL was associated with a long duration from wake-up time to bedtime (WTB, 16.5 h in SOL ≤ 30 min group and 15.8 h in SOL > 30 min group)[52]. The results showed that short SOL requires approximately 17 h of activity. Although 7 h of sleep do not guarantee 17 h of activity, 17 h of activity may provide 7 h of sleep.

2) Component #2 - Discrepancy between desired time in bed and desired total sleep time

Generally, we need 6–8 h of TST per day[54]. Nevertheless, patients with insomnia often say "I need at least 5-6 h of sleep," when they cannot fall asleep easily or maintain sleep. This merely describes how desperately they want a good night's rest. Those who wish to sleep between 5 and 6 h (desired TST) must wake up early in the morning (around 3-4 am) if they go to bed at 10 pm. By contrast, when we ask "From what time to what time do you want to sleep?", they usually reply "I want to sleep from 10 pm to 7 am (desired TIB)". In theory, the longer desired TIB may decrease sleep efficiency (SE) because it is dysfunctionally longer than the desired TST. According to the concept of sleep restriction technique in CBT-I, shortening the TIB might increase SE. The discrepancy between desired TIB and desired TST index (the DBST index) reflects the discrepancy between one's preferred hours of TIB and preferred hours of TST. According to previous reports[55,56], the DBST index can predict insomnia severity in the general population or individuals with cancer.

3) Component #3 - Time in bed during 24 hours (TIB/d)

An individual's sleep-wake pattern is measured by their bedtime and wake-up times, and their total interval of sleep (TIB) is calculated. Patients who suffer from severe illnesses, including paralysis, cancer, or renal failure, or those who undergo hemodialysis, usually spend most of their days lying

down. The usual TIB estimate does not include the time spent in bed during the day. Therefore, measuring TIB for 24 h (TIB/d) can provide insight into a person's physical activity throughout the day[57]. According to a previous study, patients with cancer with SOL > 30 min had significantly longer TIB/d than those with SOL < 30 min[58]. TIB/d can be measured by asking, "What is the average number of hours you spend lying down during 24 h, regardless of whether you sleep?"

4) Component #4 - Taking sleeping pills 7 hours before the waking-up time

Physicians frequently prescribe sleeping pills in clinical practice when CBT-I is ineffective. It is generally recommended for patients to take sleeping pills about 30 min before bedtime[59], which is followed by most patients. However, sleeping pills are generally taken 30 min before the time when most patients want to fall asleep, rather than at the time when their sleep-wake cycle indicates that they should fall asleep. Previous study[60] has found that patients with unsatisfied sleeping pills (z-drug or benzodiazepine) tended to take them at 09:16 pm and go to bed at 09:47 pm, whereas those who were satisfied tended to take them at 11:11 pm and go to bed at 11:22 pm. Sleeping pills were generally consumed within 30 min of bedtime by both groups; however, those who consumed them later were generally satisfied with them. Furthermore, patients who were satisfied with sleeping pills spent 7.1 h in bed and woke up after 7.2 h in the morning, whereas those who were dissatisfied spent 8.8 h in bed and woke up after 9.3 h. Additionally, 85%-96% of patients were satisfied with their sleeping pills when the time between the administration of sleeping pills and the wake-up time was about 7-8 h. In Korean clinical practice guidelines for management of insomnia[61], clinicians are recommended to consider educating patients to take benzodiazepines or benzodiazepine receptor agonists in time for sleep, as prescribed during CBT.

Digital therapeutic application for SIBT-I (dSIBT-I)

The four concepts of the SIBT-I can easily be incorporated into digital therapeutic application. Patients can evaluate their sleep-wake cycle in accordance with the guidelines, and an appropriate sleep-wake cycle can be determined for them. We developed a digital therapeutic application based on SIBT-I concepts (Figure 1).

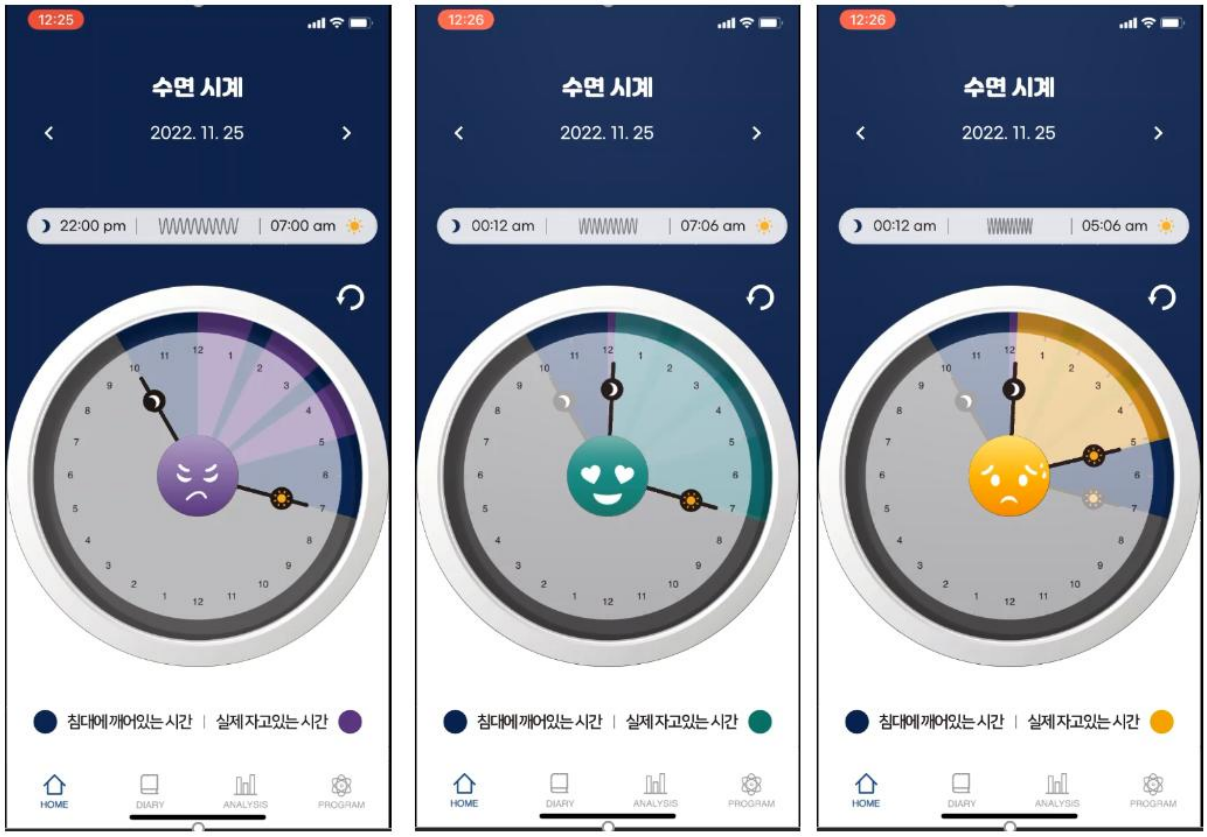

Figure 1. The digital therapeutic application of the Sleep-Index Based Treatment for Insomnia

In dSIBT-I, the clock appears on the main screen, which is different from applications that use the CBT-I. There are facial expressions and springs on the clock named “SIBT clock”.

A bright smile appears only when the patient's sleep-wake cycle is appropriate. In the case of sleep-wake cycles that are too long, the face takes on a frowning appearance. A strained facial expression can occur even when the sleep-wake cycle is too short. A spring with a low tension is displayed when the sleep-wake cycle is appropriate. However, in cases of long sleep-wake cycles, springs appear stretched and tensed. When the sleep-wake cycle is considerably long, spring breaks occur. By contrast, if the sleep-wake cycle is too short, the spring is compressed and condensed. Initially, we set a sleep-wake cycle of 7 h, but in the future, we plan to use big data to individualize it to set it accordingly.

Patients who write sleep diary entries daily can see intuitively whether the current sleep-wake cycle is appropriate. The application's main screen shows how the patient is doing based on facial expressions and springs. With dSIBT-I, patients learn sleep hygiene along with concepts of dSIBT-I instead of modules in CBT-I, such as stimulus control, sleep restriction, or cognitive therapy.

In this study, we aimed to evaluate the effectiveness and safety of dSIBT-I in individuals with insomnia. A double-blind, randomization study was conducted to compare dSIBT-I with an application which included the CBT-I.

Methods

1. Participants and procedure

The study was undertaken at the Asan Medical Center, and we assessed the effectiveness and safety of the dSIBT-I application compared with the digital Cognitive Behavioral Therapy for Insomnia (dCBT-I) application in patients with insomnia. The participants in this study were recruited through advertisements in the local community from December 2022 to January 2023. Individuals were included in the study if they met the following criteria: 1) they were diagnosed with insomnia disorder based on the DSM, 5th Edition using clinical interviews with a psychiatrist, 2) they were between the ages of 19 and 80, 3) they did not have any problems using smartphones, 4) they were rated as experiencing moderate or severe insomnia based on an Insomnia Severity Index (ISI) score ≥ 15, and 5) they did not treat their insomnia symptoms using non-pharmacological or pharmacological treatment within 3 months. Participants were excluded if they met the following criteria: 1) major psychiatric disorder, such as schizophrenia, bipolar disorder, or severe major depressive disorder, 2) having sleep disorders, such as obstructive sleep apnea syndrome or restless legs syndrome, 3) had medical conditions, including organic brain disorder and cardiovascular and respiratory diseases that limited the physical activity, 4) took medications that induced sleep disturbance, 5) had difficulty communicating, and 6) were pregnant or lactating.

Our study assumed the difference of ISI score improvements between the dCBT-I group and the control group as approximately 20%. We conducted *a priori* power calculations based on 80% power, $\alpha = 0.05$, and a dropout rate of 20%, and required sample sizes were estimated to be 25 each for both groups.

The study protocol was approved by the Institutional Review Board of Asan Medical Center (2022-1347), and patients provided informed consent before study onset. Participants were compensated with approximately 30$ as a reward for the participation.

2. Digital applications

1) dSIBT-I application

The dSIBT-I app included four sessions; 1) sleep hygiene education (week 0), 2) 17 hours of activity and 7 hours of sleep (week 1), 3) educating DBST index (week 2), 4) time in bed during 24 hours (week 3), and 5) final evaluation (week 4). Furthermore, participants could use the SIBT clock from the first entry to the application.

2) dCBT-I application

To compare the effectiveness and safety of the dSIBT-I with those of the CBT-I, we developed a digital application including concepts of CBT-I. We referred to it as the digital Cognitive Behavioral Therapy for Insomnia (dCBT-I). The dCBT-I app included four sessions; 1) sleep hygiene education (week 0), 2) stimulus control therapy (week 1), 3) sleep restriction therapy (week 2), 4) cognitive therapy (week 3), and 5) final evaluation (week 4). The dCBT-I did not provide the SIBT clock.

3. Study design

Participants were included in the study if they met the inclusion criteria through a clinical interview with a psychiatrist. They were randomly allocated into one of two applications (dSIBT-I vs. dCBT-I). At the first visit, their demographic characteristics, such as sex, age, past medical/psychiatric history, shift working, and sleep disorders were collected. In addition, their sleep indices and psychological

symptoms were assessed. They were instructed to read the sleep hygiene education (week 0) material after completing self-reported rating scales, record sleep diary every day, and complete the self-report symptoms rating scale every week until the final evaluation week (week 4). A detailed instruction for the usage of the SIBT clock was not provided to participants who were allocated into the dSIBT-I app.

4. Data collection

1) Sleep diary

Participants were instructed to record a sleep diary daily. The sleep diary asked the participants to record their bedtime (what was your bedtime last night?), sleep onset time (at what time did you finally fall asleep last night?), wake time (at what time did you finally get up in the morning?), time of getting out of bed (at what time did you finally get out of bed in the morning?), and time in bed during 24 hours (what was the number of hours you spent lying down during 24 h, regardless of whether you slept?).

Furthermore, to assess their DBST index, they were asked to record their desired TST (how many hours do you want to sleep per day?) and desired TIB (from what time to what time do you want to sleep? e.g., if a participant answered that they wanted to sleep from 11:30 pm to 7:00 am, we estimated the desired TIB as 7.5 h). The DBST index was calculated as [desired TIB] - [desired TST][56,62].

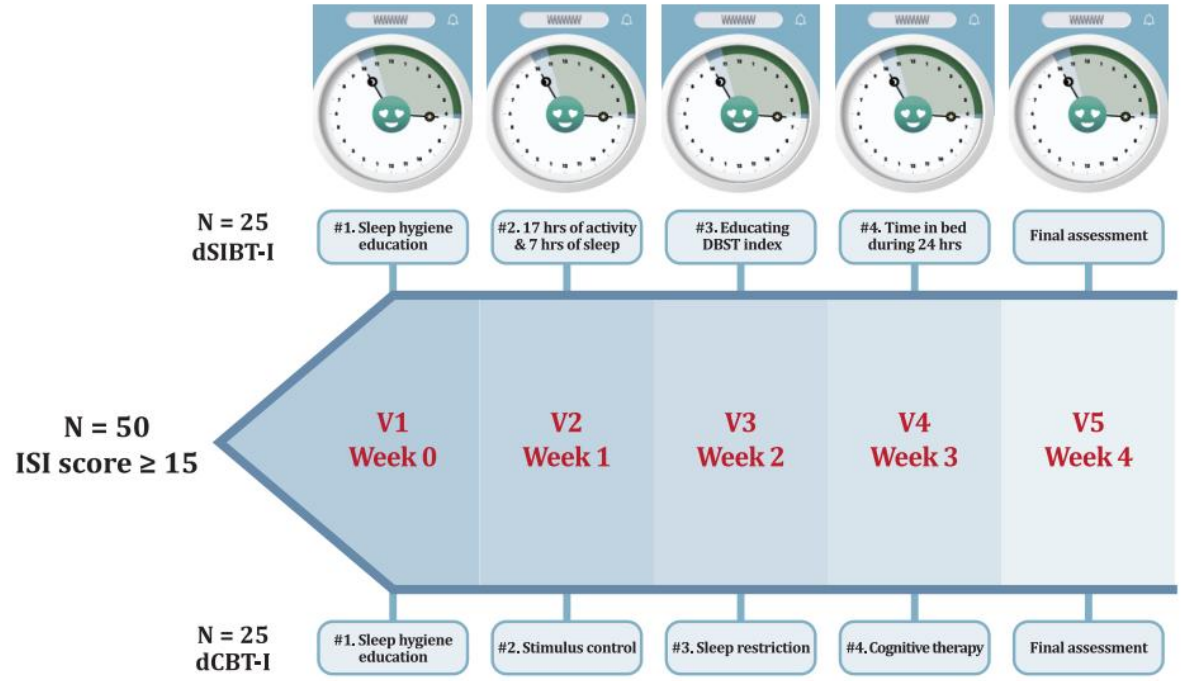

Figure 2. Study overview

2) Symptoms rating scales

Insomnia Severity Index

ISI is a self-report rating scale developed to measure the severity of individual patients' insomnia[63]. It consists of seven items, measured on a five-point Likert scale (0 = none, very satisfied, not at all noticeable, not at all worried, or not at all interfering; 4 = very severe, very dissatisfied, very much noticeable, very much worried, or very much interfering), with the total score ranging from 0-28. The degree of insomnia severity is indicated as follows: absence of insomnia (0-7), sub-threshold insomnia (8-14), moderate insomnia (15-21), and severe insomnia (22-28). In this study, we used the Korean version of the ISI scale[64].

Patients Health Questionnaire-9 items

The Patient Health Questionnaire-9 items (PHQ-9) is a self-report rating scale to measure the severity of individual patients' depression[65]. It includes nine items, each scored on a four-point Likert scale (0 = not at all; 3 = nearly every day), with the total score ranging from 0-27. A higher total score indicates a more severe degree of depression. In this study, we applied the Korean version of the PHQ-9 scale[66].

Generalized Anxiety Disorder-7 items

The Generalized Anxiety Disorder-7 items (GAD-7) is a self-report rating scale developed to evaluate the severity of individual patients' anxiety[67]. It consists of seven items, each responded to using a four-point Likert scale (0 = not at all; 3 = nearly every day), with the total score ranging from 0-21. A higher total score indicates severe anxiety. In this study, we applied the Korean version of the GAD-7 scale[68].

Dysfunctional Beliefs about Sleep-2 items

The Dysfunctional Beliefs about Sleep-2 items (DBS-2) is an ultra-brief self-report rating scale developed by our research team to evaluate patients' dysfunctional beliefs about sleep[69]. It is a modified version of the original C-DBS scale, which measures dysfunctional beliefs about sleep among cancer patients[70]. The following items are included in this scale: Q1, "My immune system will have serious problems if I do not go to sleep at a certain time" and Q2, "If I do not sleep well at night, my health status will worsen." Each item is rated using a numeric rating scale (0 = strongly disagree; 10 = strongly agree), with the total score ranging from 0-20. A higher total score reflects a higher level of dysfunctional beliefs about sleep.

WHO-5 well-being index

The WHO-5 well-being index (WHO-5) is a self-report rating scale developed to assess individual patients' psychological well-being[71]. It consists of five positively described items, each scored on a six-point Likert scale (0 = none of the time; 5 = all the time), with the raw score ranging from 0-25. The raw score is then multiplied by 4 and translated to a percentage scale ranging from 0 (absent) to 100 (maximal). A lower score indicates a worse psychological well-being. In this study, we used the Korean version of the WHO-5 scale[72].

Fatigue as a single item of numeric rating scale

The fatigue numeric rating scale (fatigue NRS) is a self-report single-item rating scale to measure the severity of individual patients' fatigue[73]. The response to the item, "What was the overall level of

fatigue you experienced during the last week?" is measured using a numeric rating scale (0 = no fatigue; 10 = severe fatigue). A higher score indicates a more severe degree of fatigue.

Satisfaction with the application

We requested the participants to evaluate their satisfaction with the digital application at V5. The evaluation was conducted in the following two aspects: Q1, "The digital application was easy to use" (usability) and Q2, "The digital application was helpful in improving sleep" (effectiveness). Both items were scored based on a five-point Likert scale (1 = not at all satisfied; 5 = very satisfied). A higher score reflects a higher level of satisfaction.

Compliance and treatment emergent- adverse events

Participants were instructed to report any adverse event during participation, such as excessive daytime sleepiness, depressed mood, anxiety, and sleep-related disabilities.

5. Statistical analysis

In this study, we recruited 50 participants with insomnia (Figure 3). After reviewing their sleep diary, we found that one participant in the dSIBT-I group and two in the dCBT-I group can be diagnosed as having Circadian Rhythm Sleep-Wake Disorders, such as advanced or delayed type. There were five dropouts in the dSIBT-I group and one in the dCBT-I group. First, we ran a linear mixed model for Intention-To-Treat and Per-Protocol analysis. Second, we analyzed the data based on outcome measures: 1) improvement of ≥ 6 in the ISI score at each visit, 2) improvement of the ISI score to less than 15 in each visit, 3) improvement of the ISI score to less than 8 in each visit, 4) satisfaction with applications in the usability and effectiveness, and 5) Treatment-Emergent Adverse Events (TEAEs). These categorical variables were analyzed using the generalized estimating equation. A summary of demographics and rating scale scores is shown as mean ± standard deviation. A significance level of $p < 0.05$ was considered two-tailed for all analyses. We employed SAS version 9.4 (Cary, NC, USA) to perform statistical analysis.

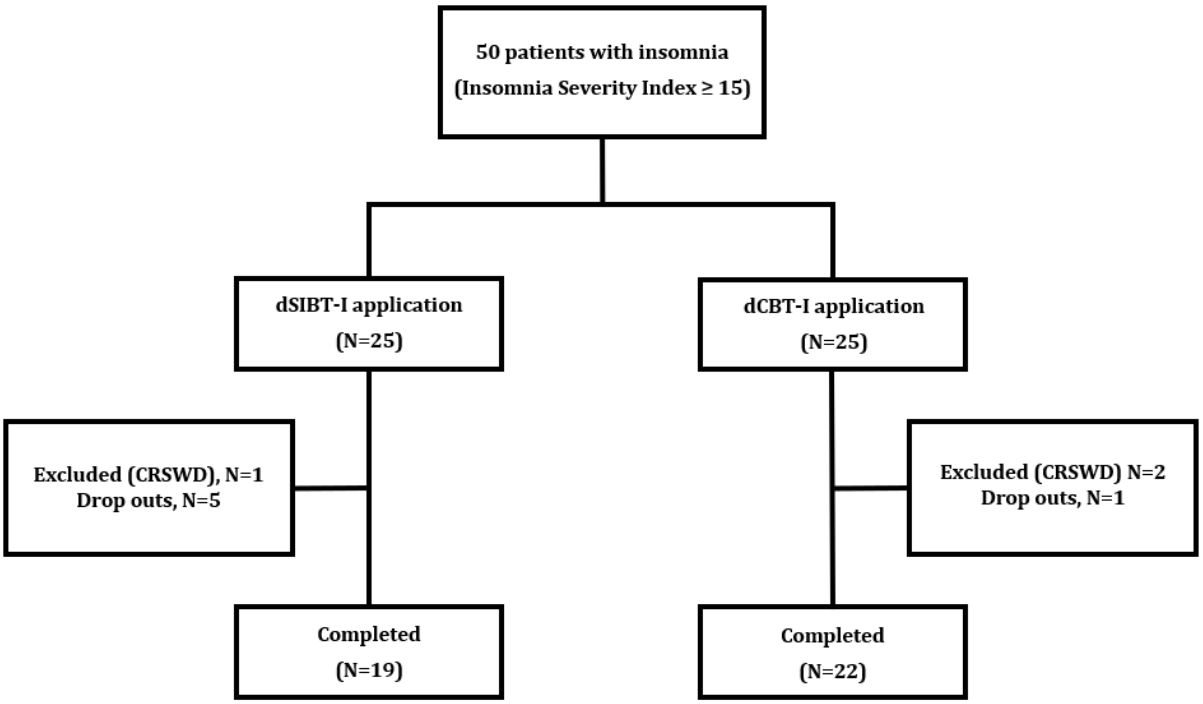

Figure 3. Flow chart of the study design

Results

Demographic characteristics

A total of 50 participants with sleep disturbance, which was measured as ISI ≥ 15, were enrolled in this study. Among the participants, 35 (70.0%) were women and their mean age was 45.0 ± 15.4 years old. At baseline, there was no significant difference between dSIBT-I and dCBT-I groups in sex, age, duration of insomnia, or symptom rating scale scores (**Table 2**). The two groups showed mean ISI scores of 17.0 ± 2.2 and 18.2 ± 3.0, respectively, both indicating a moderate degree of insomnia severity. Regarding sleep indices and the DBST index, no significant difference was observed between the two groups at baseline (**Table 3**).

Table 2. Demographic and clinical characteristics of both groups at baseline (n=50)

Variable	dSIBT-I (N=25) N (%), Mean ± SD	dCBT-I (N=25) N (%), Mean ± SD	P-value
Female gender	17 (68.0)	18 (72.0%)	0.758
Age (years)	43.7 ± 14.6	46.2 ± 16.3	0.568
Duration of insomnia (months)	52.6 ± 48.7	63.8 ± 78.5	0.555
Past psychiatric history	0 (0.0%)	1 (4.0%)	0.999
Current major medical disease	3 (12.0%)	1 (4.0%)	0.609
Habits			
Coffee during the last 2 weeks	18 (72.0%)	17 (68.0%)	0.999
Drinking during the last 2 weeks	11 (44.0%)	7 (28.0%)	0.377
Smoking during the last 2 weeks	2 (8.0%)	1 (4.0%)	0.999
Questionnaires, score			
Insomnia Severity Index	17.0 ± 2.2	18.2 ± 3.0	0.123
Patients Health Questionnaire-9 items	5.4 ± 2.9	6.6 ± 3.8	0.213
Generalized Anxiety Disorder-7 items	3.2 ± 2.5	4.4 ± 3.5	0.169
Dysfunctional Beliefs about Sleep-2 items	15.0 ± 4.3	14.4 ± 3.5	0.644
WHO-5 well-being index	45.8 ± 18.1	42.7 ± 21.2	0.588
Fatigue single item numeric rating scale	7.7 ± 1.2	7.9 ± 1.2	0.561

dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

Table 3. Demographic and clinical characteristics of both groups at baseline (n=50)

Variable	dSIBT-I (N=25) N (%), Mean ± SD	dCBT-I (N=25) N (%), Mean ± SD	P-value
Time variables			
Bedtime	11:06 ± 1:16 PM	11:27 ± 1:30 PM	0.367
Sleep onset time	12:43 ± 1:51 AM	1:08 ± 1:24 AM	0.371
Wake time	6:26 ± 1:24 AM	7:07 ± 2:16 AM	0.204
Wake-up time	7:00 ± 1:16 AM	7:42 ± 1:52 AM	0.129
Duration variables			
Sleep onset latency (min)	97.2 ± 78.6	100.8 ± 79.2	0.866
Time in bed (hr)	7.9 ± 1.4	8.2 ± 1.3	0.387
Duration from wake-up time to bedtime (WTB, hr)	16.1 ± 1.4	15.8 ± 1.3	0.387
Time in bed during 24 hours (hr)	8.0 ± 1.7	8.2 ± 2.0	0.702
Discrepancy between desired TIB and desired TST			
Desired TST (hr)	7.1 ± 0.9	6.7 ± 1.3	0.201
Desired bedtime	11:19 ± 1:04 PM	11:01 ± 0:40 PM	0.249
Desired wake-up time	6:38 ± 0:57 AM	6:37 ± 1:00 AM	0.959
Desired TIB (hr)	7.3 ± 1.2	7.6 ± 1.0	0.367
DBST index	0.2 ± 0.9	0.9 ± 1.6	0.071

TST, total sleep time; TIB, time in bed; DBST, discrepancy between desired time in bed and desired total sleep time; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

Linear mixed model analysis among all participants: Intention-To-Treat (ITT) analysis

We ran a linear mixed model analysis to explore the difference in psychiatric symptoms between the dSIBT-I and dCBT-I groups at each visit.

Insomnia severity, measured with the ISI, was significantly lower in the dSIBT-I group than the dCBT-I group at V3 ($p = 0.044$, **Table 4**). At V4, the ISI score was lower in the dSIBT-I group than the dCBT-I group, with a marginal significance ($p = 0.064$). Although there were group ($F = 3.60$, $p = 0.006$) and time ($F = 23.43$, $p < 0.001$) effects, no significant group X time interaction was observed ($F = 1.07$, $p = 0.382$).

In terms of the severity of depression measured with the PHQ-9, no significant difference in PHQ-9 scores was observed between the two groups at any visits (**Table 5**). Although there was a significant time effect ($F = 2.90$, $p = 0.032$), no group effect ($F = 1.98$, $p = 0.165$) and group X time interaction ($F = 0.37$, $p = 0.827$) were observed.

The GAD-7 score was significantly lower in the dSIBT-I group than the dCBT-I group at V4 ($p = 0.049$, **Table 6**). Although there was a significant time effect ($F = 4.15$, $p = 0.006$), no group effect ($F = 2.80$, $p = 0.101$) and group X time interaction ($F = 0.81$, $p = 0.524$) were observed.

In terms of the level of dysfunctional beliefs about sleep measured with the DBS-2 scale, there was no significant difference between the two groups at any visit (**Table 7**). In addition, there were no group ($F = 0.19$, $p = 0.668$) and time ($F = 1.16$, $p = 0.339$) effects and group X time interaction ($F = 1.60$, $p = 0.190$).

In terms of psychological well-being measured with the WHO-5 well-being index, there was no significant difference between the two groups at any visits (**Table 8**). Although there was a significant time effect ($F = 6.35$, $p < 0.001$), no group effect ($F = 1.90$, $p = 0.175$) and group X time interaction ($F = 1.22$, $p = 0.314$) were observed.

Regarding the severity of fatigue measured with a single-item NRS scale of fatigue, there was no significant difference between the two groups at any visits (**Table 9**). Although there was a significant time effect ($F = 7.42$, $p < 0.001$), no group effect ($F = 0.26$, $p = 0.611$) and group X time interaction ($F = 0.38$, $p = 0.822$) were observed.

The DBST index was bigger in the dCBT-I group than the dSIBT-I group at V1 ($p = 0.007$, **Table 10**). The DBST index was significantly lower in the dSIBT-I group than the dCBT-I group at V3 ($p = 0.012$) and V5 ($p = 0.026$). There was a significant group effect ($F = 6.15$, $p = 0.017$) and a marginally significant time effect ($F = 2.37$, $p = 0.066$). Additionally, there was a group X time effect with a marginal significance ($F = 2.27$, $p = 0.075$).

Table 4. Linear mixed model for differences in the severity of insomnia at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, p-value
Insomnia Severity Index (ISI)			
ISI at V1	17.0 ± 0.5	18.2 ± 0.5	0.115
ISI at V2	13.0 ± 0.9	14.8 ± 0.9	0.144
ISI at V3	11.5 ± 1.0	14.4 ± 1.0	0.044
ISI at V4	10.6 ± 1.1	13.3 ± 1.0	0.064
ISI at V5	10.3 ± 1.1	12.0 ± 1.0	0.269
Difference between V1 vs V2	4.1 ± 0.7	3.4 ± 0.7	0.519
Difference between V1 vs V3	5.5 ± 0.9	3.8 ± 0.9	0.182
Difference between V1 vs V4	6.5 ± 1.0	4.9 ± 0.9	0.225
Difference between V1 vs V5	6.7 ± 1.0	6.3 ± 1.0	0.790
Group effect			$F = 3.60$, $p = 0.006$
Time effect			$F = 23.43$, $p < 0.001$
Interaction group X time			$F = 1.07$, $p = 0.382$

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

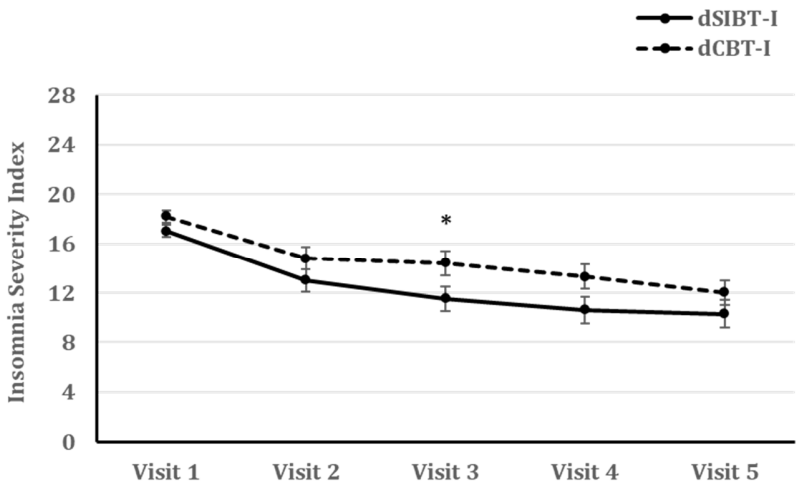

Figure 4. Changes in insomnia severity between the two groups at each visit (N=50, ITT)

Table 5. Linear mixed model for differences in the severity of depression at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, p-value
Patient Health Questionnaire-9 items (PHQ-9)			
PHQ-9 at V1	5.4 ± 0.7	6.6 ± 0.7	0.204
PHQ-9 at V2	5.1 ± 0.6	5.8 ± 0.6	0.453
PHQ-9 at V3	4.2 ± 0.7	5.5 ± 0.7	0.150
PHQ-9 at V4	4.3 ± 0.6	5.1 ± 0.6	0.362
PHQ-9 at V5	3.7 ± 0.8	5.1 ± 0.7	0.212
Difference between V1 vs V2	0.3 ± 0.5	0.8 ± 0.5	0.449
Difference between V1 vs V3	1.2 ± 0.6	1.1 ± 0.6	0.837
Difference between V1 vs V4	1.1 ± 0.6	1.5 ± 0.6	0.663
Difference between V1 vs V5	1.7 ± 0.8	1.5 ± 0.7	0.881
Group effect			F = 1.98, p = 0.165
Time effect			F = 2.90, p = 0.032
Interaction group X time			F = 0.37, p = 0.827

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

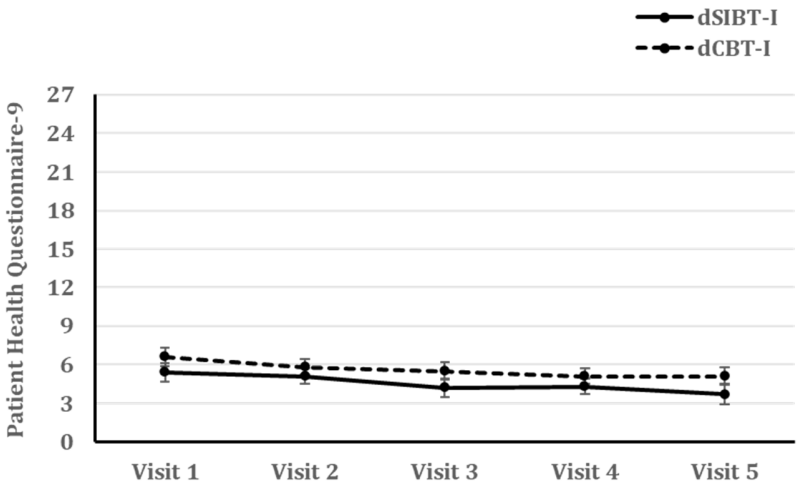

Figure 5. Changes in depression severity between the two groups at each visit (N=50, ITT)

Table 6. Linear mixed model for differences in the severity of anxiety at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, p-value
Generalized Anxiety Disorder-7 items (GAD-7)			
GAD-7 at V1	3.2 ± 0.6	4.4 ± 0.6	0.161
GAD-7 at V2	2.7 ± 0.6	3.6 ± 0.6	0.331
GAD-7 at V3	2.1 ± 0.5	2.9 ± 0.5	0.327
GAD-7 at V4	2.1 ± 0.6	3.7 ± 0.6	0.049
GAD-7 at V5	2.0 ± 0.7	3.6 ± 0.7	0.123
Difference between V1 vs V2	0.4 ± 0.5	0.8 ± 0.5	0.614
Difference between V1 vs V3	1.0 ± 0.5	1.5 ± 0.5	0.511
Difference between V1 vs V4	1.1 ± 0.5	0.6 ± 0.5	0.592
Difference between V1 vs V5	1.2 ± 0.7	0.8 ± 0.7	0.699
Group effect			F = 2.80 , p = 0.101
Time effect			F = 4.15, p = 0.006
Interaction group X time			F = 0.81 p = 0.524

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

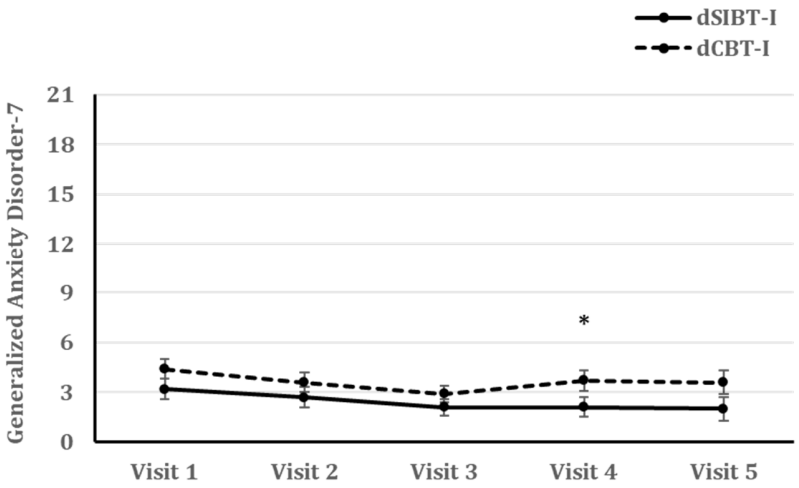

Figure 6. Changes in anxiety severity between the two groups at each visit (N=50, ITT)

Table 7. Linear mixed model for differences in the severity of dysfunctional beliefs about sleep at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, p-value
Dysfunctional Beliefs about Sleep-2 items (DBS-2)			
DBS-2 at V1	15.0 ± 0.8	14.4 ± 0.8	0.637
DBS-2 at V2	14.4 ± 0.8	14.2 ± 0.8	0.870
DBS-2 at V3	13.7 ± 0.8	14.6 ± 0.8	0.444
DBS-2 at V4	13.7 ± 0.8	14.7 ± 0.8	0.422
DBS-2 at V5	13.3 ± 0.8	14.4 ± 0.8	0.313
Difference between V1 vs V2	0.6 ± 0.6	0.2 ± 0.6	0.673
Difference between V1 vs V3	1.2 ± 0.6	-0.1 ± 0.6	0.131
Difference between V1 vs V4	1.3 ± 0.6	-0.2 ± 0.6	0.083
Difference between V1 vs V5	1.7 ± 0.6	0.1 ± 0.6	0.055
Group effect			F = 0.19, p = 0.668
Time effect			F = 1.16, p = 0.339
Interaction group X time			F = 1.60, p = 0.190

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

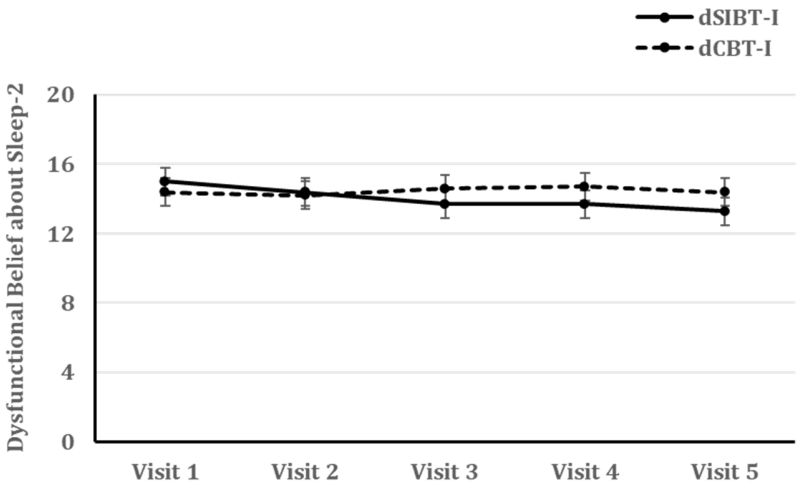

Figure 7. Changes in dysfunctional beliefs about sleep between the two groups at each visit (N=50, ITT)

Table 8. Linear mixed model for differences in the level of psychological well-being at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, p-value
World Health Organization-5 well-being index (WHO-5)			
WHO-5 at V1	40.6 ± 3.4	37.4 ± 3.4	0.506
WHO-5 at V2	46.7 ± 3.2	40.6 ± 3.2	0.183
WHO-5 at V3	50.5 ± 3.3	44.6 ± 3.2	0.205
WHO-5 at V4	53.1 ± 3.9	43.6 ± 3.8	0.087
WHO-5 at V5	52.4 ± 4.3	46.4 ± 4.2	0.324
Difference between V1 vs V2	-6.1 ± 2.3	-3.2 ± 2.3	0.379
Difference between V1 vs V3	-9.9 ± 2.9	-7.2 ± 2.8	0.505
Difference between V1 vs V4	-12.5 ± 2.9	-6.2 ± 2.8	0.119
Difference between V1 vs V5	-11.8 ± 3.6	-9.0 ± 3.4	0.575
Group effect			F = 1.90, p = 0.175
Time effect			F = 6.35, p < 0.001
Interaction group X time			F = 1.22, p = 0.314

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

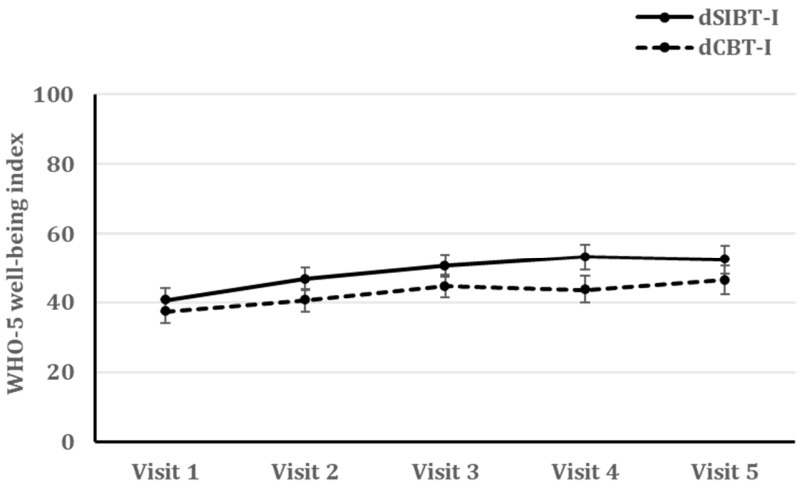

Figure 8. Changes in psychological well-being between the two groups at each visit (N=50, ITT)

Table 9. Linear mixed model for differences in the severity of fatigue at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, P-value
Fatigue single-item numeric rating scale (NRS)			
Fatigue NRS at V1	7.7 ± 0.2	7.9 ± 0.3	0.553
Fatigue NRS at V2	7.3 ± 0.3	7.5 ± 0.3	0.578
Fatigue NRS at V3	6.5 ± 0.4	6.9 ± 0.3	0.409
Fatigue NRS at V4	6.8 ± 0.4	6.6 ± 0.4	0.717
Fatigue NRS at V5	6.4 ± 0.4	6.6 ± 0.4	0.721
Difference between V1 vs V2	0.4 ± 0.2	0.4 ± 0.2	0.938
Difference between V1 vs V3	1.2 ± 0.4	1.0 ± 0.4	0.690
Difference between V1 vs V4	0.9 ± 0.3	1.3 ± 0.3	0.420
Difference between V1 vs V5	1.3 ± 0.4	1.3 ± 0.4	0.998
Group effect			$F = 0.26, p = 0.611$
Time effect			$F = 7.42, p < 0.001$
Interaction group X time			$F = 0.38, p = 0.822$

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

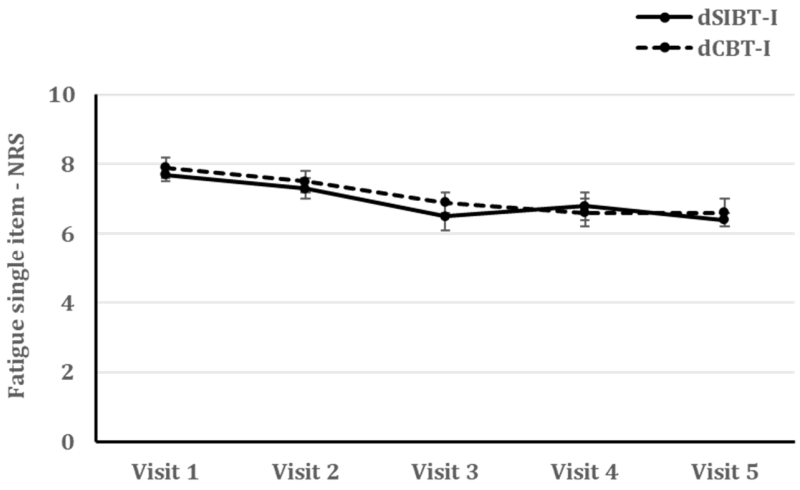

Figure 9. Changes in severity of fatigue between the two groups at each visit (N=50, ITT)

Table 10. Linear mixed model for differences in discrepancy between desired time in bed and desired total sleep time (DBST index) at each visit between the two groups (N=50, ITT)

Variable	dSIBT-I (N=25) LSM ± SE	dCBT-I (N=25) LSM ± SE	F, P-value
Discrepancy between desired time in bed and desired total sleep time (DBST index)			
DBST index at V1	0.3 ± 0.3	0.9 ± 0.3	0.007
DBST index at V2	0.08 ± 0.2	0.4 ± 0.2	0.251
DBST index at V3	-0.1 ± 0.2	0.5 ± 0.2	0.012
DBST index at V4	-0.1 ± 0.1	0.3 ± 0.1	0.084
DBST index at V5	-0.2 ± 0.2	0.4 ± 0.2	0.026
Difference between V1 vs V2	0.1± 0.2	0.5 ± 0.2	0.288
Difference between V1 vs V3	0.3 ± 0.2	0.4 ± 0.2	0.878
Difference between V1 vs V4	0.3 ± 0.2	0.6 ± 0.2	0.338
Difference between V1 vs V5	0.4 ± 0.3	0.5 ± 0.3	0.728
Group effect			F = 6.15 , p = 0.017
Time effect			F = 2.37, p = 0.066
Interaction group X time			F = 2.27, p = 0.075

LSM, Least Square Mean; SE, Standard Error; ITT, Intention-To-Treat; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

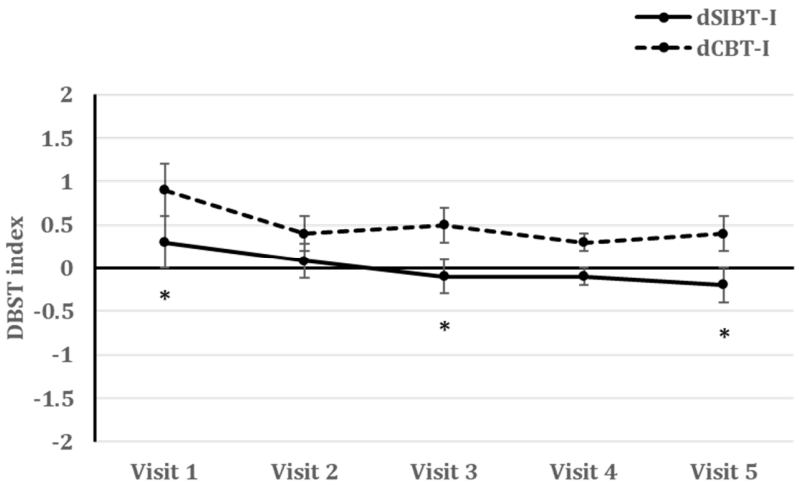

Figure 10. Changes in discrepancy between desired time in bed and desired total sleep time (DBST index) between the two groups at each visit (N=50, ITT)

Linear mixed model analysis among all completers: Per-Protocol (PP) analysis

We ran linear mixed model analysis to explore the difference in psychiatric symptoms between the two groups at each visit using data of all completers.

Insomnia severity, measured with the ISI, was significantly lower in the dSIBT-I group than the dCBT-I group at V3 ($p = 0.018$) and V4 ($p = 0.045$, **Table 11**). Although there were group ($F = 4.85$, $p = 0.034$) and time ($F = 20.24$, $p < 0.001$) effects, no significant group X time interaction was observed ($F = 0.95$, $p = 0.445$).

Regarding the severity of depression measured with the PHQ-9, there was no significant difference in PHQ-9 scores between the two groups at any visits (**Table 12**). Although there was a significant time effect ($F = 2.68$, $p = 0.049$), no group effect ($F = 0.98$, $p = 0.328$) and group X time interaction ($F = 0.31$, $p = 0.868$) were observed.

In terms of the severity of anxiety measured with the GAD-7, there was no significant difference in GAD-7 scores between two groups at any visits ($p = 0.049$, **Table 13**). Although there was a significant time effect ($F = 3.34$, $p = 0.019$), no group effect ($F = 1.50$, $p = 0.229$) and group X time interaction ($F = 0.77$, $p = 0.548$) were observed.

Regarding the level of dysfunctional beliefs about sleep measured with the DBS-2 scale, there was no significant difference between the two groups at any visit (**Table 14**). There were no group ($F = 0.19$, $p = 0.668$) and time ($F = 1.16$, $p = 0.339$) effects, but a group X time interaction ($F = 2.41$, $p = 0.007$) was observed.

In terms of psychological well-being measured with the WHO-5 well-being index, there was no significant difference between the two groups at any visits (**Table 15**). Although there was a significant time effect ($F = 6.22$, $p < 0.001$), no group effect ($F = 1.31$, $p = 0.259$) and group X time interaction ($F = 1.96$, $p = 0.121$) were observed.

Regarding the severity of fatigue measured with a single-item NRS scale of fatigue, there was no significant difference between two groups at any visits (**Table 16**). Although there was a significant time effect ($F = 6.31$, $p < 0.001$), no group effect ($F = 0.19$, $p = 0.663$) and group X time interaction ($F = 0.20$, $p = 0.935$) were observed.

The DBST index was significantly lower in the dSIBT-I group than the dCBT-I group at V3 ($p = 0.013$) and V5 ($p = 0.028$, **Table 17**). There was a significant group effect ($F = 5.93$, $p = 0.020$) and a marginally significant time effect ($F = 2.61$, $p = 0.050$). However, there was no group X time effect ($F = 1.68$, $p = 0.173$).

Table 11. Linear mixed model for differences in the severity of insomnia at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, p-value
Insomnia Severity Index (ISI)			
ISI at V1	17.2 ± 0.6	18.4 ± 0.6	0.152
ISI at V2	13.3 ± 1.0	15.5 ± 0.9	0.116
ISI at V3	11.7 ± 1.1	15.2 ± 1.0	0.018
ISI at V4	10.7 ± 1.2	14.0 ± 1.1	0.045
ISI at V5	10.1 ± 1.1	12.7 ± 1.0	0.094
Difference between V1 vs V2	3.8 ± 0.8	2.9 ± 0.8	0.415
Difference between V1 vs V3	5.5 ± 0.9	3.2 ± 0.9	0.080
Difference between V1 vs V4	6.4 ± 1.0	4.4 ± 1.0	0.155
Difference between V1 vs V5	7.1 ± 1.0	5.7 ± 1.0	0.344
Group effect			F = 4.85, p = 0.034
Time effect			F = 20.24, p < 0.001
Interaction group X time			F = 0.95, p = 0.445

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

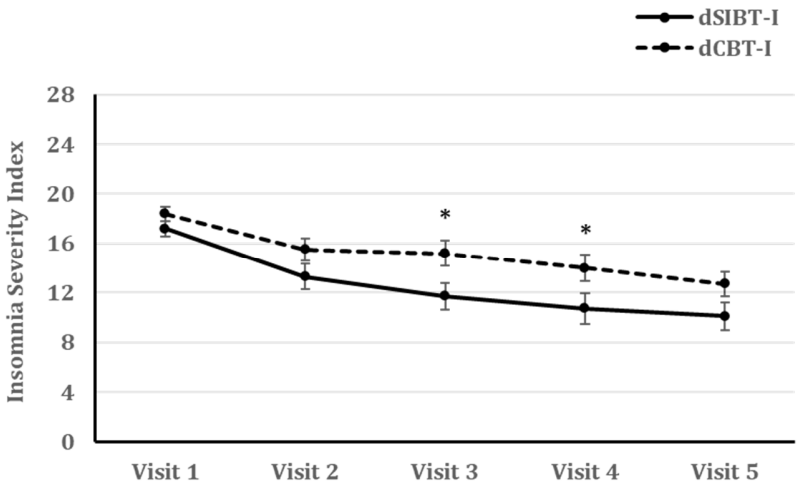

Figure 11. Changes in insomnia severity between the two groups at each visit (N=41, PP)

Table 12. Linear mixed model for differences in the severity of depression at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, p-value
Patient Health Questionnaire-9 items (PHQ-9)			
PHQ-9 at V1	5.9 ± 0.8	6.8 ± 0.7	0.424
PHQ-9 at V2	5.6 ± 0.7	5.9 ± 0.6	0.771
PHQ-9 at V3	4.5 ± 0.8	5.7 ± 0.7	0.262
PHQ-9 at V4	4.5 ± 0.7	5.3 ± 0.7	0.425
PHQ-9 at V5	4.0 ± 0.7	5.2 ± 0.8	0.344
Difference between V1 vs V2	0.2 ± 0.6	0.9 ± 0.6	0.494
Difference between V1 vs V3	1.4 ± 0.7	1.0 ± 0.6	0.734
Difference between V1 vs V4	1.4 ± 0.7	1.5 ± 0.7	0.939
Difference between V1 vs V5	1.9 ± 0.9	1.6 ± 0.8	0.831
Group effect			F = 0.98, p = 0.328
Time effect			F = 2.68, p = 0.049
Interaction group X time			F = 0.31, p = 0.868

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

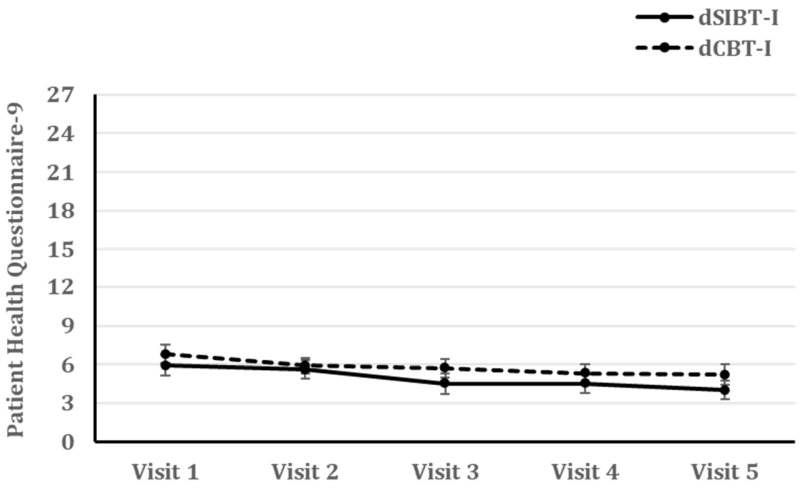

Figure 12. Changes in depression severity between the two groups at each visit (N=41, PP)

Table 13. Linear mixed model for differences in the severity of anxiety at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, p-value
Generalized Anxiety Disorder-7 items (GAD-7)			
GAD-7 at V1	3.6 ± 0.7	4.5 ± 0.7	0.404
GAD-7 at V2	2.9 ± 0.7	3.6 ± 0.6	0.490
GAD-7 at V3	2.5 ± 0.6	3.1 ± 0.6	0.471
GAD-7 at V4	2.3 ± 0.7	3.7 ± 0.6	0.119
GAD-7 at V5	2.1 ± 0.8	3.5 ± 0.8	0.201
Difference between V1 vs V2	0.7 ± 0.6	0.9 ± 0.6	0.837
Difference between V1 vs V3	1.2 ± 0.6	1.4 ± 0.5	0.786
Difference between V1 vs V4	1.4 ± 0.6	0.8 ± 0.6	0.485
Difference between V1 vs V5	1.5 ± 0.8	0.9 ± 0.7	0.557
Group effect			F = 1.50, p = 0.229
Time effect			F = 3.34, p = 0.019
Interaction group X time			F = 0.77, p = 0.548

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

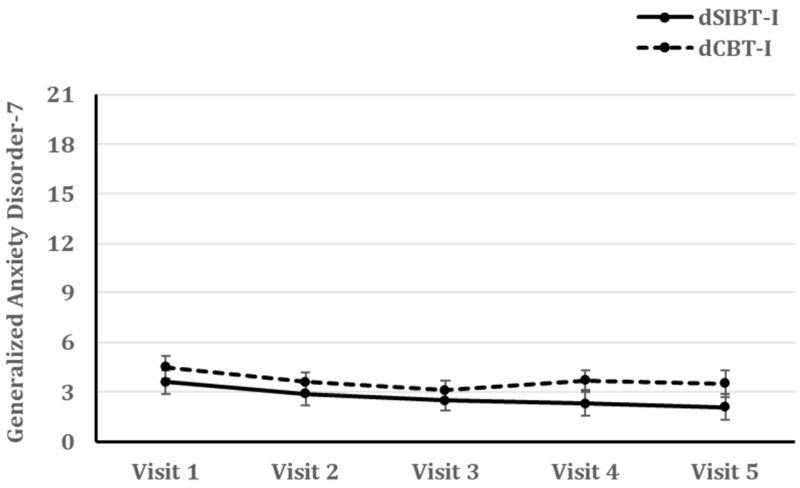

Figure 13. Changes in anxiety severity between the two groups at each visit (N=41, PP)

Table 14. Linear mixed model for differences in the severity of dysfunctional beliefs about sleep at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, p-value
Dysfunctional Beliefs about Sleep-2 items (DBS-2)			
DBS-2 at V1	15.8 ± 0.8	14.9 ± 0.7	0.365
DBS-2 at V2	15.0 ± 0.8	14.7 ± 0.8	0.778
DBS-2 at V3	14.1 ± 0.7	15.2 ± 0.7	0.258
DBS-2 at V4	14.5 ± 0.8	15.5 ± 0.7	0.353
DBS-2 at V5	13.9 ± 0.8	14.8 ± 0.7	0.431
Difference between V1 vs V2	0.8 ± 0.7	0.2 ± 0.6	0.462
Difference between V1 vs V3	1.7 ± 0.7	-0.4 ± 0.6	0.027
Difference between V1 vs V4	1.4 ± 0.6	-0.6 ± 0.6	0.026
Difference between V1 vs V5	1.9 ± 0.7	0.05 ± 0.6	0.051
Group effect			F = 0.13, p = 0.722
Time effect			F = 1.46, p = 0.232
Interaction group X time			F = 2.41, p = 0.007

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

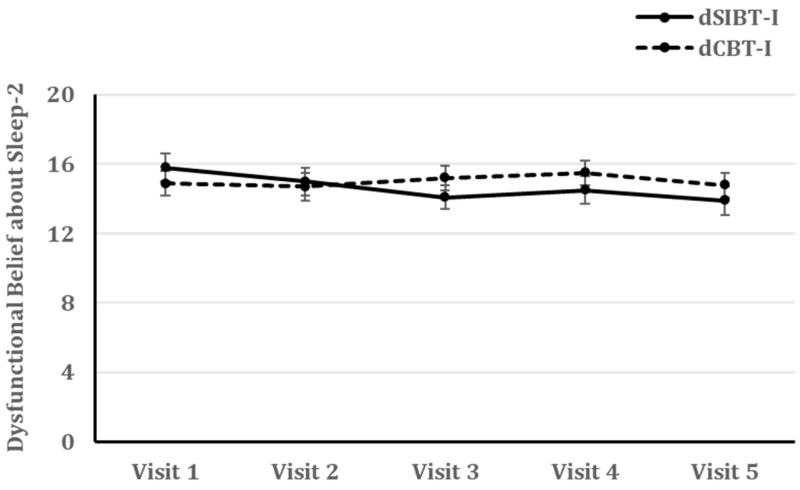

Figure 14. Changes in dysfunctional beliefs about sleep between the two groups at each visit (N=41, PP)

Table 15. Linear mixed model for differences in the level of psychological well-being at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, p-value
World Health Organization-5 well-being index (WHO-5)			
WHO-5 at V1	37.5 ± 3.8	36.9 ± 3.5	0.914
WHO-5 at V2	46.3 ± 3.4	39.5 ± 3.2	0.148
WHO-5 at V3	47.8 ± 3.4	43.5 ± 3.2	0.356
WHO-5 at V4	51.6 ± 4.3	42.2 ± 4.0	0.121
WHO-5 at V5	51.2 ± 4.8	44.9 ± 4.5	0.350
Difference between V1 vs V2	-8.8 ± 2.5	-2.5 ± 2.4	0.077
Difference between V1 vs V3	-10.3 ± 3.1	-6.5 ± 2.8	0.373
Difference between V1 vs V4	-14.1 ± 3.1	-5.3 ± 2.8	0.041
Difference between V1 vs V5	-13.7 ± 3.8	-8.0 ± 3.6	0.286
Group effect			F = 1.31, p = 0.259
Time effect			F = 6.22, p < 0.001
Interaction group X time			F = 1.96, p = 0.121

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

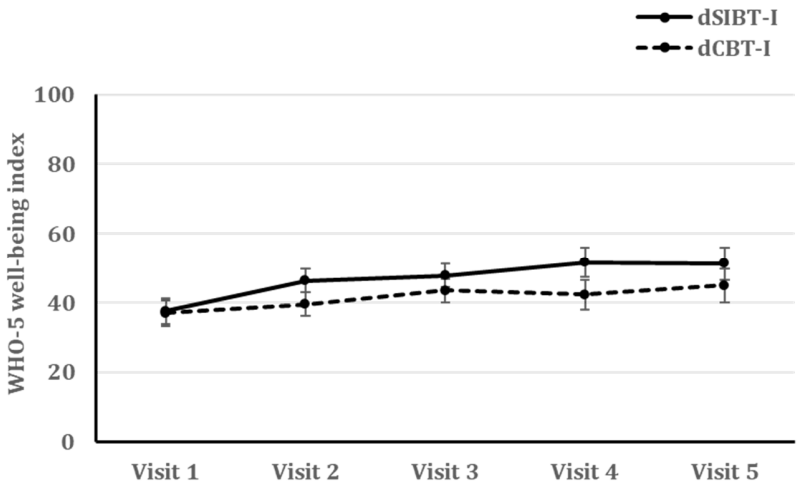

Figure 15. Changes in psychological well-being between the two groups at each visit (N=41, PP)

Table 16. Linear mixed model for differences in the severity of fatigue at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, P-value
Fatigue single-item numeric rating scale (NRS)			
Fatigue NRS at V1	7.7 ± 0.3	7.8 ± 0.3	0.925
Fatigue NRS at V2	7.3 ± 0.3	7.5 ± 0.3	0.674
Fatigue NRS at V3	6.4 ± 0.4	6.9 ± 0.4	0.431
Fatigue NRS at V4	6.8 ± 0.4	6.8 ± 0.4	0.976
Fatigue NRS at V5	6.3 ± 0.5	6.5 ± 0.4	9.767
Difference between V1 vs V2	0.5 ± 0.3	0.3 ± 0.2	0.672
Difference between V1 vs V3	1.3 ± 0.4	0.9 ± 0.4	0.483
Difference between V1 vs V4	0.9 ± 0.3	1.0 ± 0.3	0.909
Difference between V1 vs V5	1.4 ± 0.5	1.3 ± 0.5	0.826
Group effect			$F = 0.19, p = 0.663$
Time effect			$F = 6.31, p < 0.001$
Interaction group X time			$F = 0.20, p = 0.935$

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

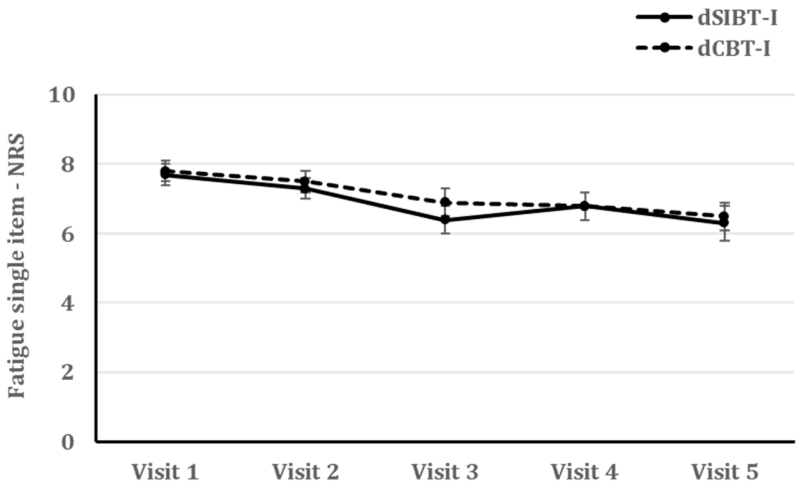

Figure 16. Changes in severity of fatigue between the two groups at each visit (N=41, PP)

Table 17. Linear mixed model for differences in discrepancy between desired time in bed and desired total sleep time (DBST index) at each visit between the two groups (N=41, PP)

Variable	dSIBT-I (N=19) LSM ± SE	dCBT-I (N=22) LSM ± SE	F, P-value
Discrepancy between desired time in bed and desired total sleep time (DBST index)			
DBST index at V1	0.3 ± 0.3	1.0 ± 0.3	0.097
DBST index at V2	0.001 ± 0.2	0.5 ± 0.2	0.121
DBST index at V3	-0.1 ± 0.2	0.6 ± 0.2	0.013
DBST index at V4	-0.1 ± 0.2	0.3 ± 0.2	0.084
DBST index at V5	-0.3 ± 0.2	0.3 ± 0.2	0.028
Difference between V1 vs V2	0.3 ± 0.3	0.5 ± 0.3	0.538
Difference between V1 vs V3	0.4 ± 0.3	0.4 ± 0.3	0.978
Difference between V1 vs V4	0.4 ± 0.3	0.7 ± 0.3	0.409
Difference between V1 vs V5	0.5 ± 0.3	0.8 ± 0.3	0.641
Group effect			F = 5.93, p = 0.020
Time effect			F = 2.61, p = 0.050
Interaction group X time			F = 1.68, p = 0.173

LSM, Least Square Mean; SE, Standard Error; PP, Per-Protocol; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

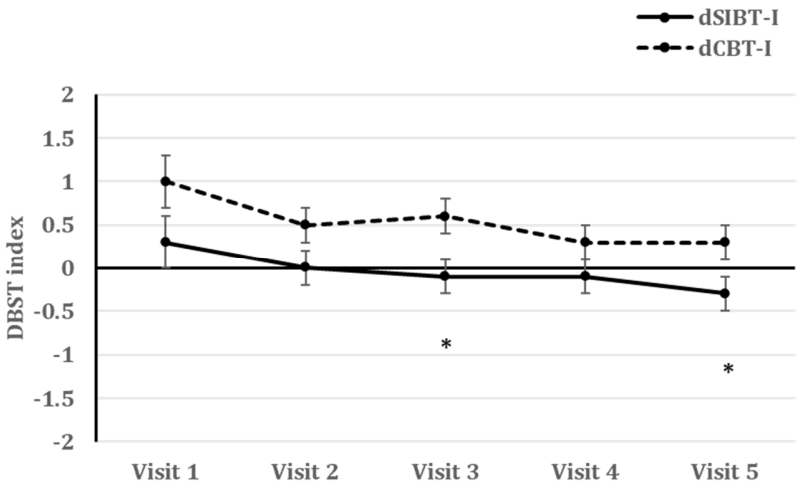

Figure 17. Changes in discrepancy between desired time in bed and desired total sleep time (DBST index) between the two groups at each visit (N=41, PP)

Outcome measures

We used a generalized estimating equation to analyze the categorical variables for outcome measures.

First, we examined the difference in the proportion of participants whose ISI was decreased ≥ 6 from baseline at each visit, whose ISI was reduced to < 15 at each visit, and whose ISI was reduced to < 8 at each visit between the two groups (**Table 18**).

Regarding the proportion of participants whose ISI was decreased ≥ 6 from baseline at each visit, there was no significant difference between two groups. There was a time effect (F=10.43, p=0.015), but there were no group (F=0.89, p=0.346) and group X time (F=0.65, p=0.885) effects.

In terms of proportion of participants whose ISI was < 15 at each visit, there was a significantly higher proportion in the dSIBT-I group than the dCBT-I group at V3 (82.6% vs. 48.0%, p = 0.017). There was a group effect (F=5.10, p=0.024), but no time (F=5.94, p=0.114) and group X time (F=1.80, p=0.615) effects.

Regarding the proportion of participants whose ISI was < 8 at each visit, there was no significant difference at any visit. In addition, group (F=0.86, p=0.355), time (F=6.95, p=0.074), and group X time (F=3.15, p=0.369) effects were not observed.

Table 18. Outcome measures at each visit

Variable	dSIBT-I group N (%)	dCBT-I group N (%)	P-value
Improvement of ≥ 6 from baseline in ISI score at each visit			
V2	9 (36.0%)	8 (32.0%)	0.765
V3	9 (39.1%)	8 (32.0%)	0.606
V4	9 (39.1%)	8 (32.0%)	0.606
V5	13 (59.1%)	12 (50.0%)	0.536
Group effect			F=0.89, p=0.346
Time effect			F=10.43, p=0.015
Interaction group X time			F=0.65, p=0.885
Improvement of ISI to less than 15 at each visit			
V1	0 (0.0%)	0 (0.0%)	
V2	16 (64.0%)	12 (48.0%)	0.254
V3	19 (82.6%)	12 (48.0%)	0.017
V4	18 (81.8%)	14 (58.3%)	0.114
V5	17 (80.95%)	15 (62.5%)	0.205
Group effect			F=5.10, p=0.024
Time effect			F=5.94, p=0.114
Interaction group X time			F=1.80, p=0.615
Improvement of ISI to less than 8 at each visit			
V1	0 (0.0%)	0 (0.0%)	
V2	3 (12.0%)	1 (4.0%)	0.609
V3	3 (13.0$)	4 (16.0%)	1.000
V4	6 (27.3%)	3 (12.5%)	0.276
V5	6 (28.6%)	5 (20.8%)	0.547
Group effect			F=0.86, p=0.355

Time effect	F=6.95, p=0.074
Interaction group X time	F=3.15, p=0.369

ISI, Insomnia Severity Index; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

Second, we assessed participants' satisfaction with application in terms of usability and effectiveness (**Table 19**). There was no significant difference between the two groups in participants' satisfaction with each application in usability and effectiveness.

Third, we collected TEAEs while using these applications. However, no TEAE was reported by the participants.

Table 19. Satisfaction with each application in terms of usability and effectiveness

	1	2	3	4	5	P-value		Mean ± SD	P-value
1) Usability									
dSIBT-I (N=20)	0	0	9	9	2	0.074		3.7 ± 0.7	0.243
dCBT-I (N=19)	0	5	6	5	3			3.3 ± 1.1	
2) Effectiveness									
dSIBT-I (N=20)	0	1	11	5	3	0.189		3.5 ± 0.8	0.240
dCBT-I (N=19)	2	1	8	8	0			3.2 ± 1.0	

Note: 1 - Not at all satisfied, 2 - Partly satisfied, 3 - Satisfied, 4 - More than satisfied, 5 - Very satisfied

SD, standard deviation; dSIBT-I, digital Sleep-Index-based Treatment for Insomnia; dCBT-I, digital Cognitive Behavioral Therapy for Insomnia

Discussion

Our study aimed to compare the effectiveness and safety between the dCBT-I, in which conventional CBT for insomnia was delivered digitally, and dSIBT-I, an alternative digital application, developed by our research team. The main characteristic of dSIBT-I was that it used concepts based on improvements of multiple sleep indices, as shown in previous studies to be important in initiating and maintaining high-quality sleep. Furthermore, to enhance compliance, we incorporated a clock with springs and different facial expressions into the digital application, which intuitively depicted the degree of appropriateness of patients' sleep-wake cycles. The results showed a significant improvement in ISI scores in both the dCBT-I and dSIBT-I groups from study initiation(V1) to completion(V5). There was no group by time interaction. However, at V3, a significant difference occurred between the two groups; the mean ISI score of dSIBT-I group was significantly lower than that of the dCBT-I group, and the proportion of participants with ISI rated below 15 was also significantly higher in the dSIBT-I group. There was no significant difference in satisfaction of participants regarding usability and effectiveness between the two groups.

The most important finding in our study was that the mean ISI score of dSIBT-I group was significantly lower than that of dCBT-I group at V3, and the proportion of participants with ISI below 15 was significantly higher in the dSIBT-I group than the dCBT-I group at that time point. This finding suggests that insomnia symptoms may improve at a faster rate when patients use the dSIBT-I application rather than the dCBT-I application. Several factors may contribute to this difference. One possible reason is the distinction of specific components of CBT between the two groups. In both groups, sleep hygiene education was conducted during the first week of therapy; however, there was a difference in the second week of treatment. In the dCBT-I group, stimulus control was the second component of therapy, whereas in the dSIBT-I group, learning and practicing the concept of "17 hours of activity and 7 hours of sleep" was the second component. Since the difference of treatment results

occurred at the third week of therapy, which is one week after the delivery of the second component, there may have been a gap in the initial effects between the two components. Although stimulus control is indeed a well-established first-line behavioral therapy for insomnia[14], patients' motivation is considered important in treatment success[74]. Adhering to multiple instructions included in stimulus control may be somewhat difficult for patients who are less motivated to participate. The concept of "17 hours of activity and 7 hours of sleep", however, can be recognized as a simple and rather clear-cut instruction even to those with lower motivation, which may have led to early treatment effects. A well-designed randomized study should be conducted in the future to compare treatment effects between the individual components.

Another potential factor is the presence of the SIBT clock in the dSIBT-I application. SIBT clocks were provided to the dSIBT-I group from the beginning of intervention. Thus, treatment effects of adjusting individual sleep patterns using the clocks may have emerged in the second week of therapy. To the best of our knowledge, this is the first study to add an intuitive item, an adjustable clock, that can be delivered through a digital application to a web-based CBT for insomnia. Previously developed platforms have also made efforts to improve patient adherence and maximize treatment outcome through animated videos and user interface, quizzes, or interactive dialogues[75]. Additional studies are necessary to examine the effects of the SIBT clock and compare it with other existing methods.

Our participants did not report any treatment-emergent adverse event. This was anticipated to some degree because digital CBT for insomnia is generally considered a safe method with minimal adverse effects. Although previous studies have reported a possibility of increased daytime sedation during initial weeks owing to sleep restriction therapy included in behavioral therapy[76], our results did not show exacerbations of daytime sleepiness measured each week by the single-item NRS scale of fatigue. This is consistent with studies examining the effectiveness and safety of other digital

applications for CBT of insomnia, in which no treatment-emergent adverse events were reported, including daytime somnolence[48].

The results of our study did not show a significant difference between the groups in patient satisfaction in terms of usability and effectiveness. The mean participant-rated scores evaluating usability and effectiveness were between 3 (satisfied) and 4 (more than satisfied), respectively, in both groups. The SIBT clock provided to dSIBT-I group participants may have been unfamiliar to the participants, especially to older adults. Nevertheless, there was no difference in patient-rated usability between the two groups, implying that the SIBT clock was not so difficult to use. As for effectiveness, the evaluation of patient satisfaction was conducted only at V5, the time point where there was no significant difference in ISI scores between the two groups. However, had we evaluated the patient satisfaction at V3, there might have been a meaningful difference between the two groups in terms of satisfaction with effectiveness, considering the difference of ISI results at that time point.

The treatment effects emerged earlier in the dSIBT-I group relative to the dCBT-I group in our study, which is important in that it shows the possibility of providing CBT to a larger population of patients with insomnia. Despite substantial evidence regarding the advantage of CBT over pharmacotherapy in terms of long-term treatment outcomes and safety[23,24,77], an important barrier to initiating the treatment is the lack of rapid treatment effects[77,78]. Owing to the negative impacts of insomnia on everyday life and complaints of significant distress by patients, many clinicians lean toward pharmacotherapy rather than CBT when choosing the initial treatment option. Even after the start of CBT, the chance of early dropout owing to low patient perseverance should be considered[32]. Our study suggests the possibility of more rapid treatment effects, which may encourage therapists to use the digital CBT as a primary treatment option for insomnia and reduce the probability of early patient dropout.

Our study has several limitations. First, although the number of participants enrolled provided sufficient power according to sample size estimations, it was relatively small especially compared with published studies verifying treatment effects of other digital applications for insomnia[48,75]. Nevertheless, our study is important as a pilot study, showing that our new digital application may result in earlier treatment effects compared with digital CBT for insomnia. Second, the mean age of participants was 45.0 ± 15.4, that is, our participants were relatively young. Considering that younger people are generally more familiar with digital applications than older adults and the prevalence of insomnia is higher in those over 65[3], the usability and effectiveness may have been rather overestimated. However, reviewing other articles, the mean age was in fact comparable to several previous studies on digital CBT for insomnia[79-81]. Third, we cannot totally rule out the chance of bias due to the order of individual treatment components. To minimize this possibility, we included sleep hygiene education at the first week of intervention for both groups and placed components of behavioral therapy immediately afterwards, that is, stimulus restriction therapy for the dCBT-I group and "17 hours of activity and 7 hours of sleep" for the dSIBT-I group. We then provided other components of behavioral therapy the following week, that is, sleep restriction for the dCBT-I group and "educating DBST index" for the dSIBT-I group. Fourth, not only was there a difference in individual treatment components between the two groups but the SIBT clock was also provided only to the dSIBT-I group. Therefore, we could not identify the factor that contributed more to treatment effects emerging more rapidly in the dSIBT-I group. Additional studies should be conducted to address this issue. Fifth, because we used a self-developed digital application as the control group, our study was not adequate to compare dSIBT-I with digital therapeutics for insomnia currently on the market, such as Sleepio or Somryst. Sixth, we excluded those who had sleep disorders, such as obstructive sleep apnea or restless leg syndrome, but because we relied on the participants' self-reports of symptoms instead of conducting polysomnography, we could not completely rule out the possibility of secondary insomnia. Lastly, our study groups did not include patients who were already

receiving pharmacotherapy. With further research, we hope to investigate treatment effects of our digital application on those patients.

Conclusions

Along with the technological advancements, new treatment modalities are appearing in the field of psychiatry, such as a digital CBT for insomnia, and our study shows the possibility of introducing a novel digital application with a relatively rapid treatment effect on insomnia. With more research, we aim to further verify its therapeutic effects and perhaps specify the potential candidates for whom our digital application can be the most effective.

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국문 요약

서론: 본 연구에서는 수면지표기반 불면증 디지털 치료기의 효과와 안전성을 평가하고, 이를 불면증 인지행동치료를 바탕으로 한 디지털 치료기와 서로 비교하고자 하였다.

방법: 본 연구는 무작위, 이중 맹검 전향적 연구로서, 서울아산병원에서 2022 년 12 월부터 2023 년 1 월까지 모집된 50 명의 환자들을 대상으로 하였다. 참가자들은 수면지표기반 불면증 디지털 치료기 집단과 불면증 인지행동치료를 바탕으로 한 디지털 치료기 집단으로 무작위 배정되었고, 평가는 1 개월간 매주 한 번씩 이루어졌다. 일차 결과지표는 4 주째의 불면증 심각도 지수였으며, 이차 결과지표는 4 주째에 불면증 심각도 지수가 15 미만인 참가자들의 비율이었다. 통계 분석을 위해 선형 혼합 모형과 일반화 추정 방정식을 이용하였다.

결과: 두 집단 모두 치료 기간동안 불면증 심각도 지수의 유의한 향상을 보였다. 4 주째의 불면증 심각도 지수와, 4 주째에 불면증 심각도 지수가 15 미만으로 감소한 참가자들의 비율 모두 두 집단 사이 유의한 차이가 나타나지 않았다. 그러나, 2 주째에는 두 가지 결과지표 모두 수면지표기반 불면증 디지털 치료기 집단에서 불면증 인지행동치료를 바탕으로 한 디지털 치료기 집단에 비해 더 우수하게 나타났다. 두 집단 모두에서 치료 이후 이상반응은 보고되지 않았다.

결론: 수면지표기반 불면증 디지털 치료기는 불면증 환자들에게 있어 불면증 인지행동치료를 바탕으로 한 디지털 치료기만큼 안전하고 효과적이며, 더 빠른 치료 효과를 보인다.