The effectiveness of digital CBT to treat insomnia in a diverse sample with insomnia disorder: A decentralized randomized controlled trial

Aric Prather, Andrew Krystal, Richard Emsley, Jenna Carl, Tali Ball, Kathryn Tarnai, Adrian Aguilera, Colin Espie, Alasdair Henry

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Abstract

Background: Cognitive Behavioral Therapy for insomnia (CBT-I) is recommended as the first-line treatment for insomnia, however, few patients can get access to it. Digital CBT-I programs have been developed and are an effective treatment, however trials often fail to enroll diverse populations.

Objective: To evaluate the effectiveness of digital CBT-I for the treatment of insomnia compared to online sleep hygiene education

Methods: This is a decentralized randomized controlled trial compared SleepioRx against online sleep hygiene (SHE) in a diverse group of 336 adults recruited nationally across the US with insomnia disorder diagnosed via structured clinical interview. Participants were allocated 1:1 to either digital CBT-I (SleepioRx) or to online sleep hygiene education (SHE). Participant recruitment occurred between November 2022 and February 2023. The primary endpoints were insomnia severity assessed using the insomnia severity index (ISI) and sleep diary sleep onset latency (SOL) and wake after sleep onset (WASO) at 10-weeks, with follow-up assessments at 16- and 24-weeks post-randomization.

Results: Compared to SHE, SleepioRx showed statistically and clinically significant improvements on the insomnia severity index (ISI) at post-treatment (10 weeks; d=0.60, p<0.001), with effects sustained at follow-up (16 weeks, d=0.65, p<0.001; and 24 weeks, d=0.77, p<0.001). SleepioRx led to significant reductions in WASO at all timepoints, however effects on SOL were not statistically significant at an adjusted alpha. Sustained statistically and clinically significant effects were observed for ISI response and remission for SleepioRx compared to SHE. SleepioRx also demonstrated improvements in mood and secondary sleep-diary outcomes.

Conclusions: The results of this trial underscore the effectiveness of digital CBT-I across patients with insomnia and reinforce that availability of FDA-cleared digital CBT-I should be expanded to increase access to first-line treatment. Clinical Trial: The trial was prospectively registered (NCT05541055) on 15 September 2022.

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Title: The effectiveness of digital CBT to treat insomnia in a diverse sample with insomnia disorder: A decentralized randomized controlled trial

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Abstract

Background: Cognitive Behavioral Therapy for insomnia (CBT-I) is recommended as the first-line treatment for insomnia, however, few patients can get access to it. Digital CBT-I programs have been developed and are an effective treatment, however trials often fail to enroll diverse populations.
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Conclusion: The results of this trial underscore the effectiveness of digital CBT-I across patients with insomnia and reinforce that availability of FDA-cleared digital CBT-I should be expanded to increase access to first-line treatment.

Trial Registration: The trial was prospectively registered (NCT05541055) on 15 September 2022.
Keywords: Insomnia; Cognitive Behavioral therapy; Randomized Controlled Trial; Digital Mental Health Treatment; Sleep

Introduction

Insomnia disorder is common, affecting approximately 10%-20% of the general population[1]. It is characterized by difficulties initiating sleep, maintaining sleep, or early morning awakening with an inability to resume sleep, which occurs at least 3 nights per week for a period of at least 3 months and is associated with significant daytime impairment[2,3]. The impacts of insomnia are significant, with patients reporting substantial reductions in quality of life[4], and experiencing elevated risk of depression[5], anxiety[5], suicide[6], and cardiometabolic disease[7,8] compared with healthy sleeping counterparts.

Cognitive behavioral therapy (CBT) is universally recommended as the first-line treatment for insomnia disorder by national and international bodies[9–12]. Despite these recommendations, fewer than 10% of patients with insomnia receive CBT, largely due to systemic barriers, including few trained therapists and poor geographical distribution of providers which limit provision at scale[13–15]. These barriers to care are more pronounced in racial and ethnic minority groups[16–18]. In practice, insomnia is typically managed using pharmacotherapy[19–21], namely FDA-approved medications (e.g., zolpidem) and/or medications prescribed off-label (e.g., trazodone), all of which can carry harmful side effects, and are associated with dependency.

A proposed solution to address limited access to CBT is for treatment to be delivered digitally, via digital mental health treatments[22,23]. A wealth of evidence exists for the effectiveness of digital CBT for insomnia (digital CBT-I), demonstrating robust effects on insomnia and sleep outcomes when compared against a range of controls[24–27]. Digital CBT-I has gained traction in recent years with two digital CBT devices now cleared by the FDA for the treatment of insomnia disorder. One of these devices, SleepioRx™, has been evaluated in 16 published randomized controlled trials (RCTs)[26,28–42], which demonstrate clinically and statistically significant improvements in key insomnia outcomes including insomnia severity and symptoms, sleep onset latency, and wake after sleep onset against a range of comparators.

Despite strong data supporting the efficacy of digital CBT-I, there are several gaps in our knowledge. First, many digital clinical trials fail to enroll participants from a diverse range of racial and socioeconomic groups, limiting the generalizability of the effects[43]. This is a common problem across clinical trials[44], and certain trial designs, such as decentralized trials, may help address barriers that limit participation by relying on remote data collection methods[45].

Secondly, although trials of digital CBT-I have assessed insomnia disorder remission, the majority, if not all, trials have assessed remission using self-reported measures that do not map closely onto current diagnostic criteria. To address these gaps, we conducted a decentralized RCT of SleepioRx versus an online sleep hygiene education (SHE) control in a diverse group of participants diagnosed with insomnia disorder confirmed by structured clinical interviews.

Methods

Study design and participants

The Clinical Effectiveness of Digital Insomnia Therapy (CrEDIT) trial was a decentralized, two-arm, investigator-blind and participant blind-to-hypothesis, parallel-group superiority randomized controlled trial (RCT) of digital CBT (SleepioRx) versus online sleep hygiene education (SHE). Participants aged 22 and older were recruited from across the United States via social media and were eligible to participate if they 1) met diagnostic criteria for insomnia disorder, confirmed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; SCID;[63]); 2) scored ≤16 on the Sleep Condition Indicator (SCI-8[64]); 3) self-reported >30 minutes sleep onset latency (SOL) and/or wake after sleep onset (WASO); 4) resided in the USA; 5) understood oral and written English and 6) were able and willing to comply with the protocol and provided informed consent. Individuals were excluded if 1) they currently received, or expected to start CBT for insomnia during study participation, or previously received CBT for

insomnia in the past 12 months; 2) if taking psychoactive medication, the dose was not stable for 5 or more half-lives; 3) if they had a past or present diagnosis of psychosis, schizophrenia or bipolar disorder, assessed via self-report and confirmed using the Mini International Neuropsychiatric Interview (MINI) for DSM-5[65], or a seizure disorder; 4) had an occupation that requires alertness/caution to avoid accidents (e.g., long-haul driver, heavy machine operator, air traffic controller, etc.); 5) reported an uncorrected hearing or vision impairment; 6) intellectual disability, or any neurocognitive or developmental disorder that would impede study participation and 7) any other condition that would not make study participation in the best interest of the participant, in the opinion of the investigator. Following randomization, there were no restrictions on usual care for either arm. Consequently, the trial was, in effect, a comparison of digital CBT for insomnia + usual care, compared to SHE + usual care. The CrEDIT trial was prospectively registered (NCT05541055; first registered 15th September 2022). The UCSF Institutional Review Board (IRB) approved this study (IRB#: 20-31243) and electronic informed consent was obtained for each participant. Study participants were compensated commensurate with their time completing assessments in the study, totaling up to $190. Participants were instructed to contact study personnel if they experienced an adverse event. There were no adverse events reported by participants.

Procedures

In accordance with a decentralized design, all study activities took place online. Recruitment ads were placed on social media platforms and shown across the US, and the racial diversity and location of recruitment were monitored and adjusted to increase the representativeness and socioeconomic and racial diversity of the sample. This was achieved by tracking the demographic characteristics of participants entering into the trial and comparing those with U.S. census data regarding demographics and socio-economic status, as well as established benchmarks for the prevalence of insomnia across age and gender groups. Adjustments were made throughout the recruitment process to target groups and regions that may be typically under-represented within clinical trials, or not represented in the enrolled trial sample.

After providing initial consent and eligibility on an online screener, potential participants were asked to complete a daily sleep diary for 10 days. Potential participants who completed 7 or more diaries were invited to a video call interview with a study coordinator during which full informed consent was obtained, the SCID and MINI were administered, and final eligibility for the trial was confirmed. Participants subsequently completed baseline assessments and were randomly assigned to receive either digital CBT-I (SleepioRx) or online sleep hygiene education (SHE). Outcomes were assessed 10-, 16-, and 24 weeks post-randomization, and at each time point, including self-reported outcomes, 10 days of sleep diaries and a video call where the SCID was administered. All outcome data were assessed and recorded using an online electronic data capture system independent of SleepioRx. Automated reminders were built into the electronic data capture system to follow-up with participants if outcome assessments were not completed for a period of 3 days. To reduce the likelihood of fraudulent participant entries, participants were required to provide a valid form of photo identification during the initial video call assessment and were asked to have their video on momentarily so their likeness could be compared against the ID they provided. Participants' identity was reconfirmed at each video assessment using the same approach. Further, each participant was allocated a unique ID number that they had to enter in prior to completing any online assessments within the electronic data capture system and provided this number at the start of each follow-up video call which provided another means of participant verification.

Routine monitoring of data collected within the electronic data capture system was conducted on a regular basis throughout the course of the trial, which included data reviews conducted every 4-6 weeks by an independent data monitor in accordance with a pre-defined trial monitoring plan to ensure data completeness and quality. Any data issues identified were raised with the principal investigator and addressed. The study was also overseen by a Data Safety and Monitoring Board

(DMSB) that met every 6 months and reviewed blinded data from the trial.

Interventions

Participants allocated to the digital CBT-I arm received SleepioRx (Big Health Inc.). SleepioRx is an FDA-cleared, fully-automated digital CBT intervention for the treatment of insomnia disorder that can be made available on the order of a licensed healthcare provider (K233577; FDA., 2024). SleepioRx delivers cognitive (e.g., cognitive restructuring and paradoxical intention) and behavioral (e.g., stimulus control, sleep restriction, and sleep hygiene) techniques tailored based on daily sleep diaries. In this study, participants could access SleepioRx for up to one year.

Participants allocated to SHE received sleep hygiene advice representative of what patients would receive in routine clinical practice. It was based on resources developed by the American Academy of Sleep Medicine[66], National Sleep Foundation[67], and the National Heart Lung and Blood Institute[68]. Specifically, the sleep hygiene advice included psychoeducation on the links between sleep and health; factors to avoid, particularly in the evening, to improve sleep (e.g., alcohol, nicotine, heavy meals, caffeine, daytime napping, late-night exercise); tips for creating a healthy wind-down routine and a sleep-friendly sleep environment. This content also mirrors information on lifestyle, bedroom, and wind-down routines provided in SleepioRx. Consistent with real-world SHE, participants received all content at once and were encouraged to revisit it throughout the course of the trial.

Outcomes

The primary endpoints were insomnia severity (assessed by the Insomnia Severity Index ISI[52]), as well as sleep-diary-based SOL, and WASO at 10 weeks post-randomization. Secondary outcomes included rates of response (change of ≥6)[69] and remission (score <8)[70] on the ISI, self-reported insomnia symptoms assessed on the SCI-8[64], and rater-assessed remission of insomnia disorder operationalized as no longer meeting diagnostic criteria on the SCID. Additional secondary outcomes included anxiety (7-item Generalized Anxiety Disorder scale [GAD-7][71]), depressive symptoms (8-item Patient Health Questionnaire [PHQ-8][72]), sleep diary total sleep time (TST), total wake time (TWT), time in bed (TIB), sleep efficiency (SE) and sleep quality (SQ). The use of concomitant treatment was recorded at baseline and all outcome time points.

Randomization and masking

Participants were randomly assigned centrally within the electronic data capture platform (1:1) to SleepioRx or SHE using block randomization with block sizes of 6. No study personnel had access to the randomization sequence. All study personnel blinded to participant allocation, and participants were blind to hypotheses, with both interventions described as “sleep programs” in all participant-facing information, and the detail provided for each arm did not reveal which was the intervention or control. Further, no indication of the directionality of the study hypotheses was provided.

Statistical analysis

Allowing for 30% attrition, a minimum 332 participants (166 per arm) were required to detect a minimum between-group effect of d=0.3 with 90% power. As recommended, a correction for 5 multiple comparisons (three co-primary outcomes [ISI, SOL, WASO], and two secondary outcomes [ISI response and ISI remission]) using a conservative Bonferroni approach gave an alpha of 0.01[73].

Primary analyses followed intention-to-treat (ITT) principles, and primary outcomes (ISI, SOL, and WASO) were analyzed using linear mixed effect models, with baseline values, categorical

time, randomized group, and a time*group interaction included as fixed effects, and participant as a random effect. Continuous secondary outcomes were analyzed using the same method. For all continuous outcomes, between-group Cohen's *d*'s were calculated based on the adjusted between-group difference divided by the pooled baseline standard deviation for the full sample on that measure. Binary secondary outcomes (ISI response and remission, SCID remission) were analyzed using logistic mixed models, and odds ratios, confidence intervals, and two-sided p-values are reported. One model per outcome was used to estimate effects at weeks 10 and 16, and effects at 24 weeks were assessed using separate models that incorporated the week 10, 16, and 24 outcomes. Clinical significance was pre-specified as between-group *d* of ≥0.5 for the ISI, and a 10% or greater absolute difference in rates of ISI response and remission between-groups, per AASM criteria.[9]

In addition to the primary ITT analyses, pre-specified complier-average causal effect (CACE) and per-protocol analyses of the primary endpoints were carried out to assess the impact of adherence to digital CBT for insomnia. Three compliance definitions were used: 1) completion of at least 1 lesson; 2) completion of at least 3 lessons, and 3) completion of all 6 lessons. All analyses were conducted using Stata v18.0 (StataCorp, 2023).

Results

Participants were recruited between November 2022 and February 2023, and of 6,499 participants that started the online screener, 470 progressed to the video call eligibility assessment, and a total of 336 participants were randomized to either digital CBT (n=168) or SHE (n=168). See Figure 1 for the study flow. As displayed in Table 1, baseline characteristics were similar across groups. Participants demonstrated clinical levels of severity in the ISI at baseline with a mean ISI score of 18.23 (SD = 3.96), and participants had a mean diary-assessed SOL of 54.11 minutes (SD=40.10) and WASO of 47.38 minutes (SD=42.15). On the SCI-8, the participants' mean score was 7.92 (SD=3.91), further indicating clinically severe impairment. Of the 168 participants allocated to SHE, 165 (98%) initiated treatment, and of those allocated to SleepioRx, 124 (74%) initiated treatment.

Figure 1: CONSORT diagram of participant study flow

Table 1: Characteristics of the study sample

Characteristic	SHE (n=168)	SleepioRx (n=168)	Sample (N=336)
Age, mean (SD),y	46.84 (9.72)	45.96 (10.09)	46.40 (9.90)
Gender, N (%)			
Women	90 (54)	98 (58)	188 (56)
Men	75 (45)	66 (39)	141 (42)
Transgender	1 (1)	1 (1)	2 (1)
Non-binary	2 (1)	2 (1)	4 (2)
Other	0	1 (1)	1 (1)
Sex at birth, N (%)			
Female	93 (55)	102 (61)	195 (58)
Male	75 (45)	66 (39)	141 (42)

Race/ethnicity, N (%)			
Asian	11 (7)	7 (4)	18 (5)
Black	13 (8)	19 (11)	32 (10)
Latinx / Hispanic	12 (7)	11 (7)	23 (7)
Multiracial	11 (7)	8 (5)	19 (6)
Middle Eastern / North African	1 (1)	0	1 (1)
Native American / American Indian / Alaska Native / Indigenous	1 (1)	1 (1)	2 (1)
Pacific Islander / Native Hawaiian	0	0	0
White	119 (71)	121 (72)	240 (71)
Not specified	0	1 (1)	1 (1)
Employment, N (%)			
Full-time employed	79 (47)	83 (49)	162 (48)
Part-time employed	21 (13)	22 (13)	43 (13)
Unemployed	22 (13)	24 (14)	46 (14)
Retired	18 (11)	15 (9)	33 (10)
Full-time student	6 (4)	6 (4)	12 (4)
Full-time homemaker or carer	22 (13)	18 (11)	40 (12)
Education level, N (%)			
No formal qualifications	1 (1)	2 (1)	3 (1)
Secondary school / high school graduate	15 (9)	11 (7)	26 (8)
Some college	55 (33)	65 (39)	120 (36)
Undergraduate / Bachelor’s degree	58 (35)	58 (35)	116 (35)
Postgraduate or professional degree	39 (23)	32 (19)	71 (21)
Marital status, N (%)			
Married	81 (48)	75 (45)	156 (46)
Divorced/Separated	34 (20)	26 (15)	60 (18)
Never married	36 (21)	51 (30)	87 (26)

Partnered	12 (7)	12 (7)	24 (7)
Widowed	3 (2)	4 (2)	7 (2)
Prefer not to say	2 (1)	0	2 (1)
Household income, N (%)			
Under 15,000	19 (11)	18 (11)	37 (11)
15,000 to 24,999	16 (10)	19 (11)	35 (10)
25,000 to 49,999	40 (24)	29 (17)	69 (21)
50,000 to 74,000	27 (16)	37 (22)	64 (19)
75,000 to 99,999	18 (11)	24 (14)	42 (13)
100,000 to 149,999	27 (16)	24 (14)	51 (15)
150,000 to 199,999	8 (5)	11 (7)	19 (6)
200,000 and over	13 (8)	6 (4)	19 (6)
Timezone, N (%)			
Eastern	80 (48)	91 (54)	171 (51)
Central	46 (27)	48 (29)	94 (28)
Mountain	16 (10)	12 (7)	28 (8)
Pacific	26 (15)	17 (10)	43 (13)
Alaska	0	0	0
Hawaii-Aleutian	0	0	0
Comorbidities*, N (%)			
Heart disease or high blood pressure	29 (17)	29 (17)	58 (17)
Diabetes	21 (13)	22 (13)	43 (13)
Stroke or other neurological problems	3 (2)	3 (2)	6 (2)
Cancer	7 (4)	8 (4)	15 (4)
Arthritis or other joint problems	36 (21)	51 (30)	87 (26)
Respiratory conditions (such as asthma, COPD)	15 (9)	22 (13)	37 (11)
Digestive disorders (such as	18 (11)	22 (11)	40 (11)

ulcers, IBS, Crohn's disease)			
Depression	53 (32)	53 (32)	106 (32)
Anxiety	44 (26)	61 (36)	105 (31)
Hormonal problems	6 (4)	6 (4)	12 (4)
Dermatological conditions	13 (7)	12 (7)	25 (7)
None	55 (33)	50 (30)	105 (31)
Other	20 (12)	27 (16)	47 (14)
Use of prescription sleep medication, N (%) Yes No	 29 (17) 139 (83)	 26 (15) 142 (85)	 55 (16) 281 (84)
Use of over the counter sleep medication, N (%) Yes No	 54 (32) 114 (68)	 63 (37) 105 (63)	 117 (35) 219 (65)
Use of ANY sleep medication, N (%) Yes No	 69 (41) 99 (59)	 77 (46) 91 (54)	 146 (43) 190 (57)
Use of other prescription medication, N (%) Yes No	 85 (51) 83 (49)	 83 (49) 85 (51)	 168 (50) 168 (50)
ISI, mean (SD)	18.33 (4.19)	18.12 (3.72)	18.23 (3.96)
WASO, mean (SD)	46.06 (31.45)	48.71 (50.71)	47.38 (42.15)
SOL, mean (SD)	53.92 (41.83)	54.30 (38.41)	54.11 (40.10)
SCI, mean (SD)	7.98 (3.91)	7.85 (3.93)	7.92 (3.91)
PHQ-8, mean (SD)	9.84 (5.04)	9.52 (4.48)	9.68 (4.76)
GAD-7, mean (SD)	6.45 (5.01)	6.12 (4.56)	6.29 (4.79)
Total time in bed (TTIB), mean (SD), minutes	570.17 (122.21)	569.40 (110.24)	569.79 (116.20)
Total sleep time (TST), mean (SD), minutes	434.57 (132.44)	419.66 (114.11)	427.12 (123.65)
Total wake time (TWT), mean	178.91 (92.69)	185.69 (107.27)	182.30 (100.15)

(SD), minutes			
Sleep efficiency (SE), mean (SD), %	70.66 (11.71)	69.21 (14.13)	69.93 (12.98)
Sleep quality (SQ), mean (SD)	2.49 (0.63)	2.48 (0.62)	2.48 (0.62)

*not mutually exclusive categories.

Treatment effects on primary outcomes

Compared with SHE, SleepioRx led to statistically and clinically significant reductions in insomnia severity (ISI) at week 10 (d=0.60; p<0.001), with maintenance of gains through weeks 16 (d=0.65) and 24 (d=0.77) (Table 2). SleepioRx resulted in a significant reduction in SOL at week 10 at an unadjusted alpha; however, this was not significant once the Bonferroni correction was applied. At weeks 16 and 24 the difference between groups on SOL was not statistically significant. SleepioRx led to statistically significant reductions in WASO at week 10 (d=0.21; p=0.003) that was maintained through the follow-up period (week 16: d=0.28; week 24: d=0.29).

Table 2: ISI, SOL, and WASO summary statistics by group and time, and estimated treatment effects at week 10 (primary outcome), week 16 (follow-up), and week 24 (long-term follow-up). Adjusted differences are between-group mean differences. p<0.01 indicates statistical significance due to correction for multiple testing.

Assessment	**Unadjusted mean (SD); n**		**Adjusted difference (SE)**	**99% CI**	**p-value**	**Cohen's d**
	SHE	**SleepioRx**				
ISI						
Baseline	18.33 (4.19); 168	18.12 (3.72); 168				
Week 10	14.74 (5.00); 156	12.11 (6.10); 138	-2.37 (0.56)	-3.81, -0.92	<0.001	0.60
Week 16	14.60 (5.19); 153	11.37 (5.67); 129	-2.55 (0.57)	-4.01, -1.09	<0.001	0.65
Week 24	14.80 (5.49); 147	11.00 (5.93); 125	-3.05 (0.59)	-4.56, -1.54	<0.001	0.77
SOL						
Baseline	53.92 (41.83); 168	54.30 (38.41); 168				
Week 10	45.54 (48.82); 157	36.75 (32.00); 132	-9.14 (3.63)	-18.49, 0.20	0.012	0.23
Week 16	38.82 (38.23); 153	32.56 (29.70); 124	-6.68 (3.69)	-16.18, 2.83	0.070	0.17

Week 24	36.49 (40.73); 147	32.80 (43.59); 122	-4.37 (3.99)	-14.64, 5.90	0.273	0.11
WASO						
Baseline	46.06 (31.45); 168	48.71 (50.71); 168				
Week 10	33.82 (30.06); 157	24.54 (21.40); 132	-8.86 (2.94)	-16.42, -1.29	0.003	0.21
Week 16	35.27 (32.75); 153	23.97 (23.32); 124	-11.69 (2.97)	-19.35, -4.03	<0.001	0.28
Week 24	35.64 (35.10); 147	24.11 (27.03); 122	-12.02 (3.19)	-20.24, -3.80	<0.001	0.29

CI=Confidence Interval; SD=Standard Deviation; SE=Standard Error

Treatment effects on secondary outcomes

At week 10, SleepioRx participants had almost 6 times greater odds of ISI remission (ISI score<8) than control participants (OR=5.78; $p<0.001$ (99% CI 2.11, 15.84); Table 3). Greater rates of remission in the SleepioRx group compared to SHE were maintained at weeks 16 and 24. Similarly, participants randomized to SleepioRx had significantly greater odds of insomnia response (ISI score reduction of ≥6) compared to SHE (Table 3). Across all time points, SleepioRx had clinically significantly higher absolute rates of response and remission relative to SHE (absolute difference between-groups ≥10%).

Blinded rater-assessed insomnia remission was evaluated by examining whether participants no longer met SCID criteria for insomnia disorder at week 10, 16, and 24. While 55% of participants in the SleepioRx group experienced Insomnia Disorder remission based on SCID interview compared to 44% of participants in the SHE group at week 10, the odds of remission by arm were not statistically significant. In contrast, SleepioRx participants were significantly more likely to no longer meet SCID criteria at week 16 than controls (OR=1.85; 0.016 (1.12, 3.04). By week 24, the difference between SleepioRx and SHE participants was no longer statistically significant (Table 3).

As displayed in Table 4, participants randomized to SleepioRx experienced significantly greater improvements on several self-reported secondary outcomes relative to SHE, namely self-reported symptoms of DSM-5 disorder (SCI-8; *d*'s 0.83-1.07; p<0.001), depression (PHQ-8) and anxiety (GAD-7). With respect to secondary sleep diary measures, SleepioRx participants reported significantly better sleep efficiency and sleep quality at all follow-up time points compared to SHE participants. There were no consistent statistically significant differences between SleepioRx and SHE participants on other sleep diary time outcomes, including total sleep time (TST), time in bed (TIB), or total wake time (TWT).

Table 3: Analysis of ISI remission and response and SCID remission

	No. (% of group)		**OR; p-value (99% CI)**
	SHE	**SleepioRx**	

ISI remission (ISI score <8)			
Week 10 – No	146 (94%)	101 (73%)	5.78; <0.001 (2.11, 15.84)
Yes	10 (6%)	37 (27%)	
Week 16 – No	139 (91%)	95 (74%)	3.49; <0.001 (1.40, 8.69)
Yes	14 (9%)	34 (26%)	
Week 24 - No	136 (93%)	88 (70%)	5.00; <0.001 (1.92, 13.03)
Yes	11 (7%)	37 (30%)	
ISI response (ISI score reduction of ≥6)			
Week 10 – No	110 (71%)	68 (49%)	2.52; <0.001 (1.33, 4.75)
Yes	46 (29%)	70 (51%)	
Week 16 – No	107 (70%)	62 (48%)	2.76; <0.001 (1.43, 5.35)
Yes	46 (30%)	67 (52%)	
Week 24 - No	96 (65%)	54 (43%)	2.92; <0.001 (1.48, 5.76)
Yes	51 (35%)	71 (57%)	
SCID remission (defined as no longer meeting diagnostic criteria)			
Week 10 – No	78 (56%)	54 (45%)	1.54; 0.086 (0.95, 2.52)
Yes	61 (44%)	65 (55%)	
Week 16 – No	70 (48%)	41 (34%)	1.85; 0.016 (1.12, 3.04)
Yes	74 (52%)	80 (66%)	
Week 24 - No	57 (42%)	36 (31%)	1.66; 0.055 (0.99, 2.80)
Yes	78 (58%)	82 (69%)	

CI=Confidence Interval; SE=Standard Error
Note: Odds ratio >1 for ISI means the odds of being in remission/response are higher in SleepioRx than Control Group.

Table 4: SCI-8, PHQ-8, and GAD-7 summary statistics by group and time, and estimated treatment effects. Effects are between-group mean differences. $p<0.05$ indicates statistical significance due to no correction for multiple testing for these outcomes.

Assessment	**Unadjusted mean (SD); n**		**Adjusted difference**	**95% CI**	***p*-value**	**Cohen's *d***
	SHE	**SleepioRx**				

			(SE)			
SCI-8						
Baseline	7.98 (3.91); 168	7.85 (3.93); 168				
Week 10	12.19 (5.49); 156	15.69 (6.88); 137	3.49 (0.67)	2.19, 4.80	<0.001	0.90
Week 16	12.68 (5.71); 153	16.06 (6.74); 129	3.24 (0.67)	1.92, 4.56	<0.001	0.83
Week 24	12.36 (6.09); 147	16.81 (7.47); 124	4.20 (0.70)	2.83, 5.56	<0.001	1.07
PHQ-8						
Baseline	9.84 (5.04); 168	9.52 (4.48); 168				
Week 10	8.44 (4.89); 156	6.91 (5.39); 138	-1.03 (0.47)	-1.94, -0.11	0.028	0.22
Week 16	9.26 (5.51); 153	6.74 (5.08); 129	-1.61 (0.47)	-2.54, -0.68	<0.001	0.34
Week 24	9.05 (5.73); 147	6.56 (5.53); 125	-1.53 (0.49)	-2.50, -0.56	0.002	0.32
GAD-7						
Baseline	6.45 (5.01); 168	6.12 (4.56); 168				
Week 10	6.81 (5.12); 156	5.42 (4.83); 137	-1.03 (0.46)	-1.92, -0.14	0.024	0.22
Week 16	7.03 (5.24); 153	5.57 (4.74); 129	-0.84 (0.46)	-1.75, 0.06	0.069	0.18
Week 24	7.14 (5.90); 147	5.18 (4.88); 125	1.28 (0.48)	-2.22, -0.34	0.008	0.27
TIB (time in bed, mins)						
Baseline	570.17 (122.21); 168	569.40 (110.24); 168				
Week 10	554.96 (102.63; 157	567.06 (158.20); 132	17.35 (13.39)	-8.90, 43.60	0.195	0.15
Week 16	542.61 (106.45); 153	538.15 (115.59); 124	-2.46 (13.66)	-29.22, 24.31	0.857	0.02

Week 24	543.93 (99.00); 147	544.77 (105.75); 122	3.90 (13.03)	-21.65, 29.44	0.765	0.03
TST (total sleep time, mins)						
Baseline	434.57 (132.44); 168	419.66 (114.11); 168				
Week 10	449.48 (128.29); 157	471.45 (186.39); 132	28.97 (15.21)	-0.85, 58.79	0.057	0.23
Week 16	433.92 (116.92); 153	456.77 (116.62); 123	28.42 (15.52)	-2.00, 58.83	0.067	0.23
Week 24	446.89 (134.76); 147	456.48 (125.26); 122	19.04 (15.34)	-11.02, 49.10	0.214	0.15
TWT (total wake time, mins)						
Baseline	178.91 (92.69); 168	185.69 (107.27); 168				
Week 10	146.60 (86.18); 157	133.90 (123.08); 129	-11.92 (11.41)	-34.28, 10.43	0.296	0.12
Week 16	144.37 (94.43); 153	119.70 (102.12); 124	-23.49 (11.56)	-46.15, -0.83	0.042	0.23
Week 24	128.97 (77.02); 146	118.54 (99.14); 122	-10.49 (11.10)	-32.25, 11.26	0.345	0.10
Sleep efficiency (0-100)						
Baseline	70.66 (11.71); 168	69.21 (14.13); 168				
Week 10	75.33 (13.23); 157	78.04 (14.12); 129	2.95 (1.39)	0.21, 5.68	0.035	0.23
Week 16	75.59 (13.47); 153	80.02 (12.23); 123	4.31 (1.41)	1.54, 7.08	0.002	0.33
Week 24	77.11 (12.65); 146	79.71 (13.73); 122	2.83 (1.41)	0.07, 5.59	0.044	0.22
Sleep quality (0-5)						
Baseline	2.49 (0.63); 168	2.48 (0.62); 168				
Week 10	2.86 (0.70); 155	3.09 (0.82); 129	0.25 (0.08)	0.09, 0.41	0.002	0.40
Week 16	2.83 (0.72); 155	3.14 (0.80); 127	0.29 (0.08)	0.13, 0.45	<0.001	0.46

Week 24	2.91 (0.78); 147	3.16 (0.82); 122	0.24 (0.08)	0.07, 0.40	0.005	0.38

Impact of adherence on primary outcomes

Per-protocol and Complier-Average Causal Effect (CACE) analyses of the primary endpoints assessed the impact of adherence to SleepioRx. Increased adherence was associated with greater improvements in ISI, SOL, and WASO scores compared to SHE. Further, the demographics of participants across each of the compliance measures were largely consistent.

Post-hoc analyses

Initial analyses revealed that study participants, on average, reported at least 7 hours of sleep, which is higher than several other similar trials[31,46,47] and could indicate minimal room to move on SOL and WASO despite high overall insomnia severity. Thus, we carried out post-hoc analyses to evaluate the effects of SleepioRx on the primary endpoints in participants with sleep duration of ≤6.5 hours. Treatment effects in this cohort were larger than those observed in the ITT sample (see Supplemental Table S5).

Further post-hoc analyses were conducted on ISI response and remission outcomes to evaluate robustness of effects to missing data under worst plausible assumptions (see Tables S6 and S7). These analyses demonstrate that SleepioRx continues to lead to statistically and clinically significant differences in rates of remission relative to control.

Discussion

The primary goal of this study was to test the effectiveness of digital cognitive behavioral therapy (SleepioRx) in a large, diverse sample of adults diagnosed with insomnia disorder. Consistent with our hypotheses, participants allocated to SleepioRx showed significant and sustained improvements in insomnia symptoms compared to a sleep hygiene control condition. Individuals randomized to SleepioRx also showed improvements in diary-based measures compared to the control condition, including fewer minutes awake after sleep onset and shorter sleep onset latency, though the latter was not statistically significant after correction for multiple comparisons. In secondary analyses, SleepioRx also produced improvements in diary-assessed sleep efficiency and subjective sleep quality. Given the significant need for effective treatments to address insomnia symptoms, these data provide further support for the role of digital CBT-I in tackling this need.

To our knowledge, this is the first study to investigate whether digital CBT for insomnia predicts remission of insomnia disorder using structured clinical interviews. Here, we found some evidence that participants randomized to SleepioRx were less likely to meet diagnostic criteria for insomnia disorder compared to the control condition, though this was only statistically significant at the 16-week time point. Findings were stronger when remission was assessed using the ISI remission criteria (i.e., ISI score of <8), and indeed, greater than the pre-specified clinically significant difference threshold, though absolute rates of remission were slightly lower than found in a recent meta-analysis (30% vs 41%[48]. This difference may be the result of the diverse sample included in this study that had individuals from underserved backgrounds who may experience greater barriers to care that impact treatment outcomes (e.g.[17]). Remission rates using the SCID were high in both the SleepioRx and SHE conditions, with smaller between-group differences than seen in other measures. This may be due to the binary nature of the SCID to establish disorder presence versus absence. Further, regression to the mean, which is often a concern in clinical trials[49], may have had an outsized impact on the SCID outcome as compared to our other insomnia outcome measures. Unlike measures like the ISI and SCI-8, remission status on the SCID occurs if a participant fails to meet even one of the diagnostic criteria (e.g., reduction to less than 3 nights per week of disturbance in the

past 3 months). Future work should further explore the utility of using diagnostic criteria to establish insomnia remission. It is likely, however, that both patient-reported and clinician-reported measures could be used in tandem when evaluating outcomes.

We also found that SleepioRx produced considerable and largely sustained improvements in symptoms of depression and anxiety compared to the control condition. Our findings are consistent with the growing literature showing that digital CBT for insomnia, including SleepioRx, can lead to significant reductions in depressive and anxiety symptoms[5,50,51].

A key strength of this study was the regional, racial, and socioeconomic diversity of the study sample. Indeed, the demographic composition of the sample closely mapped the US population with regard to gender[52], education attainment[53], income[54], and employment status[55]. Although the racial characteristics of the sample did not map directly to the US population[56], it had greater racial diversity than observed in many other CBT trials (e.g.,[32,57]). The results demonstrate sustained benefits to sleep in a population of individuals with likely greater life stressors and barriers to accessing and adhering to care (e.g.,[16,17]). Indeed, although other studies have had more racially diverse samples (e.g., [30]), these have been limited to single-site designs and have not recruited participants from across the US. Further, many other studies of digital CBT either have very homogeneous samples (e.g., [34]), or fail to report details regarding participant demographics and SES characteristics. Future trials should build upon this work and evaluate whether there are differential treatment engagement or responses in appropriately powered subsample analyses.

Related to the above, the diversity of this study underscores the potential for decentralized trials for the evaluation of digital mental health treatments. The use of decentralized trials has proliferated in recent years, largely catalyzed in response to the COVID-19 pandemic[71]. This trial shows that decentralized designs can be used effectively to evaluate the effectiveness of digital mental health treatments and that such designs may support greater diversity and increase inclusivity in trials[45].

A further strength is the *a priori* multiplicity adjustment, nevertheless, Bonferroni corrections are known to be highly conservative[58] and therefore may have increased the likelihood of Type II errors. Had an alternative, less conservative method been used (e.g., Holm-Bonferroni procedure)[59], statistical significance would have been observed for all five powered outcomes in ITT analyses.

Despite the many strengths of this study, there are several limitations. First, the study sample was recruited via social media and may not reflect the general population or patients seeking treatment through healthcare providers. Relative to other trials, participants reported longer sleep duration and lower SOL and WASO at baseline, despite meeting diagnostic criteria for insomnia disorder / chronic insomnia, which does not require a minimum SOL or WASO duration[2,3], which may have limited the ability to detect improvement in SOL and WASO specifically. In addition, our follow-up period ended at 24 weeks post-randomization, and we cannot infer benefits sustained beyond that point. That said, other studies support treatment benefits as far out as 3 years after starting digital CBT-I[60]. Finally, a slightly higher drop-out was observed in those randomized to the SleepioRx condition as compared to the SHE condition, though this is common in digital therapy studies, and results were robust to worst-case plausible assumptions relating to missing data[32,57].

This study reinforces the clinical effectiveness and potential of digital treatments like SleepioRx. Indeed, this has been recognized by the Centers for Medicare and Medicaid Services (CMS) which has defined a new category of evidence-based digital mental health treatments (DMHTs), which includes SleepioRx and other FDA-cleared interventions for insomnia and mental health conditions. This has involved the creation of new codes permitting reimbursement for these treatments which is a significant step towards increasing scalable access to evidence-based, first-line CBT-I.

In conclusion, this decentralized RCT found that digital CBT-I (SleepioRx) was effective at treating insomnia disorder in a diverse sample of adults diagnosed with insomnia disorder compared to sleep hygiene education. Data show that digital CBT for insomnia is cost-effective compared to

other treatments[61] and that it can be implemented at scale[62]. Further efforts should be made to increase the availability of evidence-based digital CBT-I to expand provision of first-line treatment for insomnia disorder.

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Data Availability: The datasets generated and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Author Contributions: AP, AK, JRC, TMB, CAE, KT, AA, and ALH conceptualized the study; AP, AK conducted the study; RE carried out the statistical analyses; AP, ALH drafted the paper; all authors provided feedback and revision; all authors have read and approved the manuscript.

Abbreviations:
CACE = Compiler Average Causal Effect
CBT-I = Cognitive Behavioral Therapy for Insomnia
DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
FDA = Food and Drug Administration
GAD-7 = 7-item Generalized Anxiety Disorder Scale
ISI = Insomnia Severity Index
ITT = Intention to treat
PHQ-8 = 8-item Patient Health Questionnaire
RCT = Randomized Controlled Trial
SCI-8 = Sleep Condition Indicator
SCID = Structured Clinical Interview for DSM-5
SHE = Sleep Hygiene Education
SOL = Sleep Onset Latency
TIB = Time in bed

TST = Total Sleep Time
TWT = Total Wake Time
WASO = Wake After Sleep Onset

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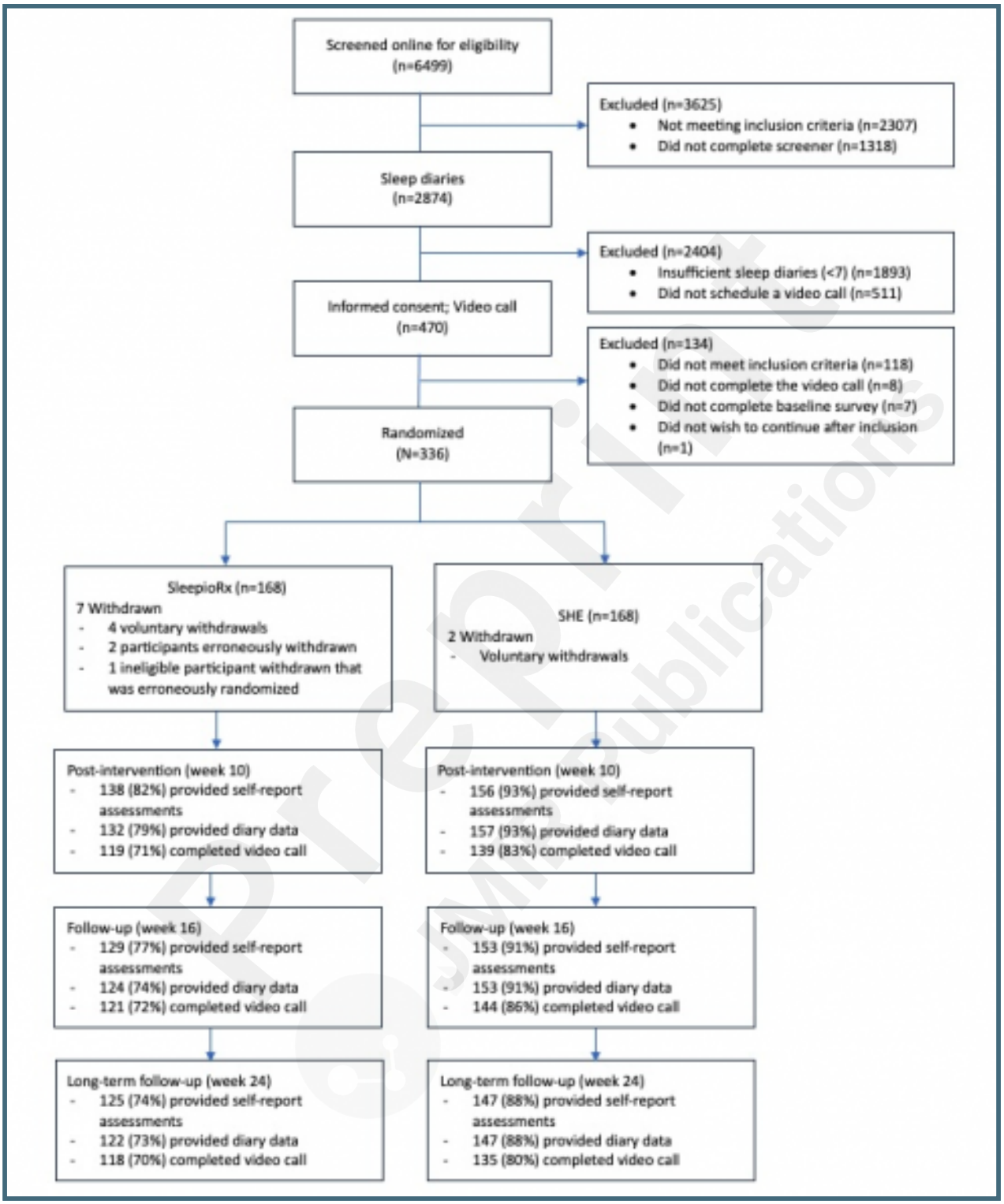
Supplementary Files

Figures

Consort diagram.



CONSORT (or other) checklists

CONSORT checklist.
URL: http://asset.jmir.pub/assets/41f664e5f524cd86beea928b078791c0.pdf