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Comparison of Multimodal Delivery of Cognitive Behavioral Therapy for Insomnia in Middle Aged Adults: A Randomized Clinical Trial Design and Methodology

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Abstract

The recommended first-line treatment for insomnia is cognitive behavioral therapy for insomnia (CBTi), but access is limited. Telehealth- or internet-delivered CBTi are alternative ways to increase access. To date, these intervention modalities have never been compared within a single study. Further, few studies have examined a) predictors of response to the different modalities, b) whether successfully treating insomnia can result in improvement of health-related biomarkers, and c) mechanisms of change in CBTi. This protocol was designed to compare the three CBTi modalities to each other and a waitlist control for adults aged 50-65 years (N = 100). Participants are randomly assigned to one of four study arms: in-person- (n=30), telehealth- (n=30) internet-delivered (n=30) CBTi, or 12-week waitlist control (n=10). Outcomes include self-reported insomnia symptom severity, polysomnography, circadian rhythms of activity and core body temperature, blood- and sweat-based biomarkers, cognitive functioning, and magnetic resonance imaging.

Keywords: Chronic Insomnia disorder; Treatment; Cognitive Behavioral Therapy for Insomnia; Middle-aged adults; Mechanisms of change

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Introduction

Insomnia is a widespread sleep problem, with 20% of adults experiencing symptoms of insomnia and approximately 10% (i.e., ~34 million U.S. adults) meeting diagnostic criteria (Chung et al. 2015; Morin and Jarrin 2022). As many as 80% of episodes of insomnia last more than a year (Sateia et al. 2000) and 40% last five years or more (Morin et al. 2020). Insomnia causes significant suffering (Léger and Bayon 2010), and is a risk factor for post-traumatic stress disorder, depression, anxiety, adjustment disorders, suicide, alcohol and substance abuse, anger, and aggression (Taylor et al. 2003; Taylor et al. 2016), inflammation (Slavish et al. 2018; Walker et al. 2020), faster genetic (Gill et al. 2015; Mithani et al. 2021) and brain aging (Osorio et al. 2011), worse cognitive functioning (Wardle-Pinkston et al. 2019), and physical health (Taylor et al. 2007). Healthcare costs (i.e., physician visits, prescriptions, and other treatment) associated with insomnia were estimated at $13.93 billion in 1995 (Walsh and Engelhardt 1999) and $92 - $107 billion in 2010 (Rosekind and Gregory 2010).

The gold-standard, non-pharmacological cognitive behavioral therapy for insomnia (CBTi) is considered the first-line treatment of insomnia (Morgenthaler et al. 2006; Qaseem et al. 2016; Wilson et al. 2010). Meta-analyses support the efficacy of therapist-delivered CBTi in both uncomplicated insomnia (Morin et al. 1994; Murtagh and Greenwood 1995; Okajima et al. 2011) and insomnia comorbid with other disorders (Geiger-Brown et al. 2014; Smith et al. 2005; Taylor and Pruiksma 2014). Despite the large base of support for CBTi, many people with insomnia fail to receive the treatment, in part due to a lack of providers trained in CBTi (Thomas et al. 2016; Zhou et al. 2021). Thus, medications are the most common insomnia treatment, but several studies have shown that CBTi is as effective as medication in the short-term (Health June 13-15, 2005; Wilt et al. 2016), with considerably better long-term outcomes (Edinger and Sampson 2003; Edinger et al. 2001; Jacobs et al. 2004; Morin et al. 1999; Sivertsen et al. 2006). Further, the use of hypnotics to treat insomnia more than doubles the risk of developing dementia (Chen et al. 2012).

With the onset of the COVID-19 pandemic and related strains, much of clinical practice has transitioned to telehealth-delivered CBTi, typically delivered via commercially available videoconferencing software. This is an excellent way to bring the therapy to patients who may not have a nearby clinician trained in CBTi. Recent studies compared in-person- to telehealth-delivered CBTi (Arnedt et al. 2021; Gehrman et al. 2021) and generally found non-inferiority.

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Results showed that telehealth-delivered CBTi was still slightly less effective (average *d* = -.10) than in-person delivered. Several commercially available internet-delivered CBTi treatments have also been designed to fill the therapist gap. However, two head-to-head comparison studies found internet-delivered CBTi is about half as effective (average difference *d* = -.50) as in-person delivered CBTi (Kallestad et al. 2021; DJ Taylor, Peterson, A. L., Goodie, J. L., Grieser, E., Hryshko-Mullen, A. S., Rowan, A., Wilkerson, A., Pruiksma, K. E., Dietch, J. R., Hall-Clark, B., Fina, B. 2019; Taylor et al. 2017). Similarly, another group compared in-person versus guided (i.e., therapist contact) internet-delivered CBTi and found an even larger difference in effects (d = 1.1; Lancee et al. 2016). To our knowledge, no study has compared the various modalities of CBTi (e.g., in-person-, telehealth-, and internet-delivered) in a single study, which is an essential scientific step in establishing best evidence-based practice. In addition, few studies have been adequately powered to investigate individual differences that determine who responds best to which CBTi modality. It is unclear for whom these telehealth- and internet-delivered interventions are best and if there is greater dropout than for in-person therapy modalities when used in the real world. Randomized clinical trials in this domain typically recruit specifically for individuals *willing* to do telehealth- or internet-delivered CBTi, but in the real-world patients may be prescribed these treatments with no regard for preferences, which could predict treatment outcomes.

Many studies have also observed links between insomnia and greater inflammation (Slavish et al. 2018; Walker et al. 2020) and blood-based neurodegenerative biomarkers (Osorio et al. 2011) as well as worse cognitive functioning (Wardle-Pinkston et al. 2019), and functional brain activity (Kay and Buysse 2017; Nofzinger et al. 2004; Sabot and Baumann 2023). Therefore, it is plausible that improving insomnia will also improve potentially more salient consequences of insomnia such as cognitive functioning, neuroplasticity, and neurodegenerative biomarkers (i.e., glial fibrillary acidic protein [GFAP], neurofilament light chain [NF-L], tau, and ubiquitin carboxy-terminal hydrolase L1 [UCH-L1]) outcomes. This study investigates whether CBTi can improve inflammation, cognitive functioning, neurodegenerative biomarkers, and neuroplasticity. Biomarkers thought to mediate poor health related to insomnia may vary between responders and non-responders.

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Research Design

The primary aim of this study is to address barriers associated with accessing psychological treatment for insomnia (Kay and Dzierzewski 2024) by comparing the effectiveness of different CBTi delivery modalities and determining which individual differences predict greater treatment effectiveness. Specifically, this study aims to determine if in-person CBTi is superior to telehealth- (tCBTi) or internet-delivered (Sleep Healthy Using the Internet [SHUTi]) CBTi on self-reported insomnia symptom improvement (i.e., Insomnia Severity Index [ISI]; *primary outcome*). The primary hypothesis is that in-person CBTi will outperform both tCBTi and SHUTi, and that all treatment groups will result in greater insomnia improvement (decreased ISI) compared to WLC.

Exploratory aims of this study are to examine 1) whether successful amelioration of insomnia (regardless of treatment arm) mediates improvements in a host of sleep, circadian, blood- and sweat-based biomarkers, cognitive functioning, multimodal neuroimaging, health and psychosocial measures and 2) predictors of response to the different modalities. A final, multipronged aim was to 1) establish feasibility and acceptability of recruiting and randomizing patients to four arms, 2) determine our ability to collect, store and analyze the objective assessments (e.g., in-home polysomnography [PSG] and core body temperature, blood- and sweat-based biomarkers, cognitive functioning, neuroimaging), 3) determine facilitators and barriers of implementing the various interventions, and 4) track changes to the protocol necessary for implementation.

Methods and Procedures

This protocol describes a four-arm randomized design (see Figure 1) implementing variable-length CBTi (i.e., 6-12 sessions depending on good end-state, defined as SE > 90% and ISI ≤ 7) across three treatment arms—1) in-person- (CBTi), 2) telehealth- (tCBTi), and 3) internet-delivered CBTi (SHUTi)—compared to a waitlist control (WLC) group (Figure 1). All study procedures are approved and monitored by the University of Arizona's Institutional Review Board (IRB# 2107024013). This study is preregistered with clinicaltrials.gov (NCT05226585).

Participants

We aim to recruit 100 adults aged 50-65 with complaints of insomnia from the local community by word of mouth, referrals from local behavioral health and sleep medicine professionals, Facebook advertisement, newspaper, and flyer postings. This age range was chosen because this

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is typically the earliest age of onset for neurodegenerative biomarkers (e.g., Amyloid-β) to begin expressing themselves and thus treatment-related changes may be detectable within this age range (Chen et al. 2018). It is not feasible to use the presence of these biomarkers as inclusion criteria.

Inclusion Criteria. Recruited participants are between the ages of 50-65, meet DSM-5 criteria for insomnia, speak and read English sufficient for informed consent and treatment, have access to a computer with sufficient internet speed, video and audio capabilities, live within a 45-minute drive of the University of Arizona, agree to remain within the area for six months following first baseline assessment, and are willing to refrain from new external behavioral health or medication treatment for issues pertaining to sleep throughout the duration of the study.

Exclusion Criteria. Exclusion criteria include the following: failure to meet inclusion criteria, current circadian rhythm disorder, inadequate sleep opportunity (e.g., ≤ 7 hours average time in bed), hypersomnia or other related sleep disorders (assessed via blinded clinical interview and self-report), untreated sleep disordered breathing (e.g., obstructive sleep apnea [OSA]), evidence of mild cognitive impairment, ineligibility for 3T Magnetic Resonance Imaging ([MRI] e.g., internal ferrous metal, metal work), fear of needles, elevated suicide risk, pregnancy, sleep efficiency >85%, and serious mental illness (e.g., bipolar disorder or psychosis).

Measures

Virtually all assessments (Table 1) in this study are widely used, have well documented psychometric profiles, and are in compliance with, and extend beyond, those deemed essential in the recommendations of the consensus conference on the assessment of insomnia in clinical trials research (Buysse et al. 2006). More detailed descriptions of the measures can be found in Supplement A.

Screening. Demographics, self-report criteria for insomnia disorder (American Psychiatric Association 2013; Espie et al. 2014), and inclusion and exclusion criteria are assessed via an online screening portal using a HIPAA-compliant REDCap server. REDCap is a secure web application for building and managing online and offline research study data, which are used for all phases of online data capture; described below (Harris et al. 2019; Harris et al. 2009). Participants who meet minimal screening criteria are asked to sign an online informed consent form via REDCap describing the study in detail.

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Baseline Part 1. After online consent, participants schedule a virtual interview to occur in 7 or more days, and complete seven days of online daily ***sleep diaries,*** sent via REDCap. Virtual interviews are then conducted with doctoral- or graduate-level evaluators via Zoom Health (HIPAA secure), blind to future treatment arm.

Baseline Part 2. Trained independent evaluators re-review the study details and informed consent form with participants to ensure continued interest. Evaluators review data from the participant's last seven days of sleep diaries to ensure average sleep efficiency ≤ 85% (i.e., minimally significant insomnia). A Montreal Cognitive Assessment (MoCA English 8.1) is then administered to exclude participants who have significant cognitive impairment (i.e., total score < 26). A Structured Clinical Interview for DSM-5 Sleep Disorders-Revised (SCISD-R; Taylor et al. 2018) is then administered to ensure participants meet criteria for insomnia disorder and to exclude participants with other sleep disorders. A Mini International Neuropsychiatric Interview (M.I.N.I.) is then administered to exclude participants with serious psychiatric diagnoses (e.g., psychosis, bipolar disorder) or high suicide risk. Participants passing this clinical interview are asked to complete an online self-report questionnaire battery via REDCap (see "Self-Report Battery" in Table 1 and Supplement A for a complete list). The battery includes subjective insomnia symptom severity assessment as well as secondary self-report psychological health outcomes.

Objective Baseline and Post-Treatment. Participants who are eligible based on Baseline Part 2 assessments are scheduled for the Objective Baseline, performed over the course of 24 hours during weekdays only. These procedures are duplicated at approximately 13 weeks following Baseline. Below is the approximate schedule.

7:00 pm (1900 hours) on a Monday, Tuesday, or Wednesday evening: Participants either come to the sleep research laboratory or research staff go to the participants' home to attach an ambulatory PSG unit ((Zmachine® Synergy; Kaplan et al. 2014) to collect single-channel electroencephalography, pulse plethysmography (i.e., heart rate) and oximetry (i.e., oxygenation saturation), nasal airflow, and chest respiratory rate to measure sleep architecture and cardiorespiratory indicators of obstructive sleep apnea (OSA; i.e., apnea-hypopnea index [AHI]). Participants are also asked to use a wrist-worn accelerometer and light sensor (Philips Respironics Actiwatch Spectrum) to measure light exposure, sleep and activity patterns for one

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week, beginning on the evening of Objective Baseline. During this visit, a sweat patch is attached to the participant's abdomen for overnight sweat collection.

1:00 pm (1300 hours) the following day: Participants arrive at the sleep research lab to return PSG equipment and complete the remainder of the Objective Baseline assessments. Device-specific software (i.e., Synergy Client Software) is used to autoscore sleep stages and respiratory events to determine AHI. Participants with an AHI of greater than or equal to 15 are excluded, as this indicates probable OSA of moderate or greater severity (Asghari and Mohammadi 2013). For participants who are not excluded, a staff phlebotomist performs blood draws, which are frozen at -80C° until assayed (see Supplement A for details).

Next, research staff administers a repeatable cognitive functioning assessment of motor function, executive functioning, and episodic memory (Wardle-Pinkston et al. 2019) using the iPad-based NIH EXecutive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER; Kramer 2014). Next, participants complete a 45-minute session of multimodal MRIscans in a 3-Telsa Siemens MRI, including a T1-weighted structural scan, a resting-state functional (T2*) scan, a task-based functional (T2*) scan while performing the Multisource Interference Task (MSIT), and lastly a single-shell 72-direction diffusion-tensor imaging scan of structural white-matter tractography. The MSIT task measures behavioral inhibition, which is a sub-domain of executive function (Bush et al. 2003). Participants are then fitted with an Equivital Harness and swallow a Vital Sense capsule, which monitors core body temperature over the next 24 hours. The sweat patch is removed at the end of the visit and immediately frozen at -80C° until assayed (see Supplement A for details).

Random Assignment

Once participants meet all criteria and complete baseline assessments, they are randomized using REDCap Randomization Module with an allocation table composed of randomly permuted blocks of 10 and 20 to ensure an allocation ratio of 3:3:3:1 per block, with a 30% likelihood of being assigned the active treatment and 10% likelihood of being assigned to the control group.

All participants in the active treatment arms receive at least six core modules of CBTi in one of three ways: 1) in-person-delivered with a clinician (CBTi), 2) via telehealth-delivered with a clinician (tCBTi), 3) internet-delivered via the SHUTi application. In the clinician-based treatments, participants can continue in treatment for an additional one to six sessions (up to 12 total), depending on ISI and sleep efficiency scores, evaluated weekly. In the SHUTi group,

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participants have a self-paced schedule to complete the six main modules and add any additional modules during the 12-week treatment period. The WLC participants wait approximately 12 weeks, after which they can begin CBTi. A review of the components of CBTi and the session breakdown for both CBTi and SHUTi are described in Supplementary Materials B and C.

In-Person- (CBTi) and Telehealth-delivered CBTi (tCBTi)

CBTi focuses on addressing maladaptive sleep habits (e.g., spending excessive time in bed, irregular sleep schedule, naps, engaging in sleep incompatible behaviors) with sleep restriction or compression (when deemed appropriate for the individual by a clinician or clinical supervisor; e.g., excessive daytime sleepiness, increased fall risk, high sleep anxiety) and stimulus control, reducing hyperarousal with relaxation strategies, and challenging maladaptive sleep beliefs and assumptions with cognitive therapy. The treatment typically consists of 6 weekly 50-minute therapy sessions administered in-person. Core content is covered in the first 5 sessions of treatment (see Supplements B and C). The final session (i.e., 6-12) is determined by the patient meeting good end-state (i.e., SE $\geq$ 90% and ISI $\leq$ 7). Sessions six through final focus on troubleshooting stimulus control, sleep restriction, relaxation, cognitive therapy, problem solving and relapse prevention, as needed.

The tCBTi study arm is identical to in-person CBTi except for the modality of treatment, which is provided via Zoom Health. Telehealth CBTi has been shown as non-inferior to in-person treatment (Arnedt et al. 2021; Gehrman et al. 2021) and could reduce access issues by allowing clinicians to provide broader-reaching treatment.

Internet-Delivered CBTi Through Sleep Healthy Using the Internet (SHUTi) Application

SHUTi is an internet-delivered, fully automated, online CBTi program delivered over six 30-minute modules, designed for use without external support. SHUTi has been validated in several randomized clinical trials (e.g., Christensen et al. 2016; Nazem et al. 2023; Ritterband et al. 2009; Ritterband et al. 2017; Zhou et al. 2022) and is arguably one of the most researched internet-delivered CBTi programs to date. The intervention tailors content delivery based on each participant's baseline sleep, treatment adherence, and progress and includes personalized interactive features: goal setting, graphical feedback based on self-reported data, animations/illustrations to enhance comprehension, patient vignettes, and video-based expert explanations. At the start of each session, the program reviews progress and evaluates the prior sleep diary.

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Waitlist Control (WLC)

Participants assigned to the WLC group wait 12 weeks for treatment. Most insomnia patients must often wait even longer to get state-of-the-science CBTi due to lack of trained providers. During this time the participants are asked to maintain their regular schedule. At the end of 12 weeks, they completed the Objective Post-Treatment and Self-Report Battery again, which serves as the baseline assessment for the WLC period. Next, they will then receive the CBTi treatment protocol. The Self-Report Battery administered at follow-up serves as the WLC Post-Treatment assessment.

Clinician Training, Certification, and Supervision

Treatment is provided by trained doctoral- or graduate-level protocol therapists at the University of Arizona, under the clinical supervision of the principal investigator (PI) Dr. Taylor (Licensed Clinical Psychologist, Board Certified in Behavioral Sleep Medicine, Fellow of the Society of Behavioral Sleep Medicine). Clinicians complete online training in CBTi (i.e., www.CBTIweb.org) and two treatment certification cases, outside of the study and under supervision, prior to treating consented study participants. Sessions are audio/video recorded (using standard consent for electronic recordings of participants) and saved to Box Health (a HIPAA compliant server), to be reviewed remotely for training, supervision, and fidelity rating purposes. To ensure fidelity and the highest possible care, clinicians receive weekly supervision on each treatment case. Modified CBTi treatment and fidelity rating scales were adopted from Taylor and colleagues (DJ Taylor, Wilkerson, A., Hryshko-Mullen, A.S., & Goodie, J.L. 2019). Fidelity ratings are performed on an ongoing basis by consultant clinical psychologists who have performed this task for other studies (Emert et al. 2023; Taylor et al. 2020).

Three-month Follow-up Assessments

The three-month follow-up assessment is a repeat of the Self-Report Battery (Table 1) completed during Baseline Part 2 and Post-Treatment. The follow-up assessment is minimal, due to the high rates of attrition for in-lab follow-up procedures, which often render the collected data unusable.

Statistical Analysis Plan

Primary Aim

First, a series of linear mixed-effects models (LMM) will be performed with the primary insomnia variables (e.g., diary sleep efficiency and ISI) as the outcomes. Diary data will be used as the primary outcome because it will be collected daily from Baseline through treatment and

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Post-Treatment (approximately 42-84 timepoints, depending on duration of therapy), giving us the maximum possible power. The ISI, one of the most common self-report measures of insomnia severity, will be given at Baseline Part 2, weekly during treatment, at Post-Treatment and Follow-Up. This will also provide high levels of power, albeit lower than the sleep diary. LMM allows the use of all data, without having to replace missing data, leading to a high-powered examination of treatment effect estimates. In both cases (i.e., sleep efficiency and ISI), estimates of the outcome variable and treatment effects will be reported.

Exploratory aim

Exploratory aims of this study are to examine 1) whether successful amelioration of insomnia (regardless of treatment arm) mediates improvements in a host of sleep, circadian, blood- and sweat-based biomarkers, cognitive functioning, multimodal neuroimaging, health and psychosocial measures and 2) predictors of response to the different modalities. Given that we expect improvements in insomnia due to CBTi for most participants, and because we are attempting to treat to good clinical end-state, all participants will be included in statistical models developed for our Exploratory Aim. We will develop repeated measures correlation plots to visualize the common within-individual association for paired measures assessed on two time periods for participants using the R-package *rmcorr*. We will compare changes in sleep efficiency and ISI with changes in cognitive functioning, neuroimaging, and neurodegenerative biomarkers using *rmcorr* models. One of the advantages of *rmcorr* is its relatively strong statistical power, given that it does not involve averaging nor aggregation to investigate an intra-individual research question. The sign of the *rmcorr* coefficient is indicated by the direction of the common regression slope. The assumptions of *rmcorr* parallel those for general linear model techniques with the exception that independence of errors is relaxed. Other assumptions (e.g., linearity, IID errors, errors normally distributed) will be examined and transformations will be conducted if appropriate. Another advantage of *rmcorr* for the Aim 2 data is that it captures intra-individual relationships between two variables that is missed by using averaged data. We will develop models for and control for the familywise error rate using the Holm-Bonferroni sequential method, which will ensure a cumulative type 1 error rate of 0.05.

In addition, we will examine and characterize with descriptive statistics the effect of CBTi modality in terms of early good end-state responders (<4 sessions), standard good end-state responders (6 sessions), late good end-state responders (7-10 sessions), or non-responders

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(after either 10 sessions or 12 weeks of treatment).

Feasibility Aim

Qualitative and descriptive statistics will be reported on 1) the feasibility and acceptability of recruiting and randomizing patients to the four arms, 2) the ability to collect, store, and analyze the objective assessments (e.g., in-home PSG and core body temperature, blood- and sweat-based biomarkers, cognitive functioning, neuroimaging), 3) the facilitators and barriers of implementing the various CBTi modalities, and 4) the changes to the protocol necessary for implementation.

Power Analysis

Statistical power calculations were developed using G*Power (Faul et al. 2009). Parameter estimates, including target effect sizes, were based on the project teams' previous research and similar studies in the medical literature. The power modeling was focused on a sufficient sample size for our primary aims and providing a sufficient sample for the exploratory analyses. Note that our primary approach to investigate the impact of treatment is an intent-to-treat (ITT) analysis. According to McCoy "Intention-to-treat analysis is a method for analyzing results in a prospective randomized study where all participants who are randomized are included in the statistical analysis and analyzed according to the group they were originally assigned, regardless of what treatment (if any) they received" (McCoy 2017). Regulatory bodies have emphasized that an ITT analysis should be the primary method for determining the effectiveness of an intervention because it allows scientists to derive unbiased conclusions regarding the trial and preserves the benefits of randomization. In contrast, a per-protocol analysis only includes participants who completed the trial's treatment protocol. Our power models focused on the ITT models while allowing for a sufficient sample to explore estimates for a per protocol analysis.

Primary Aim: Determine if In-Person-delivered CBTi is superior to Telehealth- or Internet-delivered CBTi

The primary aim is to compare three therapeutic modalities of CBTi based on changes in weekly ISI. At the time of the previous effort, no study had ever assessed differences among in-person-, telehealth-, and internet-delivered CBTi, so it was difficult to determine an acceptable clinically significant difference. Assessing outcomes multiple times over the course of treatment has the advantages of 1) increasing the confidence in the ITT analyses and 2) increasing power to find significant results, with smaller sample sizes (Vickers 2003). However, most behavioral

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randomized clinical trials focus on pre- and post-treatment assessments only. Our power analyses determined that with 14 repeated measures (i.e., baseline, 12 weeks of treatment, post-treatment), and a very conservative estimated effect size of $f = .10$ (i.e., small), there is sufficient power ($1\text{-}\beta = 0.83$) to find a significant difference between groups at alpha =.05, with an $n = 90$ divided between the 3 active treatment groups. To control for threats to internal validity, we also included a WLC group, using a 3:3:3:1 ratio as described above. This unbalanced design will result in a WLC of $n = 10$, which with an effect size ≥ 1.0 (typical from previous studies; e.g., DJ Taylor, Peterson, A. L., Goodie, J. L., Grieser, E., Hryshko-Mullen, A. S., Rowan, A., Wilkerson, A., Pruiksma, K. E., Dietch, J. R., Hall-Clark, B., Fina, B. 2019; Taylor et al. 2017) would still provide sufficient power ($1\text{-}\beta = 0.85$) to find significant differences between each of the active treatment groups and the WLC at alpha = .05. Accordingly, we plan to recruit a sample size of approximately $N = 100$ ($n = 30$ per arm and $n = 10$ in the WLC group).

Exploratory Aims. We wanted to assess and analyze many exploratory outcomes and mediators. The goal of these analyses is to determine if there is a treatment effect across the multiple outcomes and predictors of response to the different modalities. Unlike previous studies, our study is variable length which allows more time and sessions for improvement that patients slower to respond may need. By extending the original treatment (reported on above) from 6 sessions to 12 sessions, this protocol allows much more improvement in insomnia symptoms in those late responding patients. This provides more power in determining if *successful* treatment of insomnia results in benefits in a host of sleep, circadian, blood- and sweat-based biomarkers, cognitive functioning, neuroimaging (i.e., magnetic resonance and diffusion tensor imaging), and health and psychosocial measures (see Figure 1, Table 1, and Supplement A). Moving from a standard duration of treatment also allowed for robust analyses examining predictors of who responded to the various modalities and how fast they responded. Factors of interest included, but are not limited to, age, comorbidities, homework adherence, expectancies, and treatment preference. Finally, we are also interested in exploring potential mechanisms of change of CBTi, such as strengthening circadian amplitudes, measuring specifically rhythms of physiological signals known to have a 24-hour phase, such as core body temperature heart rate, and activity levels (i.e., actigraphy).

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Conclusions

The primary aim of the current study is to compare the effectiveness of three modalities of CBTi to one another as well as to a WCL group. Exploratory aims of this study are to examine 1) whether successful amelioration of insomnia (regardless of treatment arm) mediates improvements in a host of sleep, circadian, blood- and sweat-based biomarkers, cognitive functioning, multimodal neuroimaging, and health and psychosocial measures and 2) whether individual differences in these measures predict treatment response to three different CBTi modalities. Physiological and psychological measures used in this study design have been previously associated with insomnia in observational studies and are proposed meditators of the risk insomnia poses to poor health. Comparison between the treatment groups with this broad range of multimodal outcomes will also facilitate the examination of mechanisms of change important to CBTi delivery.

This study design and assessments address key questions in the sleep field pertaining to the role psychological factors have in the evaluation and treatment of sleep disorders (Kay and Dzierzewski 2024). Specifically, self-report surveys on psychological and health throughout treatment as well as during baseline and posttreatment allow investigation of the role that psychological factors are playing in sleep symptomatology and treatment response. Moreover, this study design also facilitates examination of multiple metrics of physiological functioning associated with insomnia disorder that may improve in response to CBTi, a psychologically based treatment approach. While other studies have provided some insight into the effect CBTi has on neuroimaging, none have examined both peripheral (i.e., core body temperature, immune, neurodegenerative blood-based biomarkers) and central markers (i.e., MRI, PSG) of neurophysiological health. This study is uniquely poised to examine the bidirectional relationship between psychological and neurophysiological factors involved with insomnia symptom maintenance and improvement.

Although previous research already shows that in-person-delivered CBTi is more effective than internet-delivered CBTi and is non-superior to telehealth-delivered CBTi in reducing insomnia symptoms, much less attention has been given to understanding individual differences that may be influencing the therapeutic effectiveness of the three delivery formats. We chose to extend treatment length up to 12 sessions to provide as much improvement as possible in insomnia symptoms in as many patients as possible. This has the added benefit of helping us

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determine how best to treat insomnia, and what predicts better or faster response, and then to determine if successful treatment of insomnia results in changes in exploratory biomarkers. A variable length treatment is also more ecologically valid and provides us with the most reasonable expectation of insomnia treatment success (while also balancing patient burden), and will simultaneously allow us to empirically examine what, if any, other moderators predict CBTi treatment course in this sample.

Feasibility

An ancillary aim of this research design is to use CONSORT (Thabane et al. 2016) guidelines for pilot randomized controlled trials to 1) establish feasibility and acceptability of recruiting and randomizing patients to the four arms, 2) determine our ability to collect, store and analyze the objective assessments (e.g., in-home PSG and core body temperature, blood- and sweat-based biomarkers, cognitive functioning, and neuroimaging), 3) determine facilitators and barriers of implementing the various interventions, and 4) track changes to the protocol necessary for implementation.

Potential barriers to feasibility currently identified include limitations imposed by Baseline and Post-Treatment in-lab visits, MRI safety exclusions, comorbid OSA, and the length of the protocol (i.e. three months). Participants are required to be near the university to make travel to in-lab assessments feasible. This location inclusion criterion is also in place to facilitate in-person CBTi, for those randomly assigned to this arm. Only individuals with greater than moderate OSA were excluded, due to the high rates of insomnia and OSA comorbidity, which may affect target recruitment goals. Text and email reminders and weekly well-being checks will be used to keep participants engaged in the study and encourage completion of assessments throughout their 3-month involvement in the study.

Summary

While we know that CBTi works to treat insomnia, questions remain as to how treatment is working to improve insomnia, which modalities work best, for whom, and duration needed for an individual to recover. This study addresses the connection between insomnia and health difficulties by sampling variables across multiple psychological and physiological domains thought to modulate treatment response to CBTi and by allowing treatment to extend beyond the six fundamental modules. Data generated from this clinical trial will be instrumental in providing

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guidance for case conceptualization and evidence-based practice in the treatment of chronic insomnia disorder among middle-aged adults. The experimental design comparing multiple modalities of CBTi delivery with variable treatment length will also facilitate the investigation of more basic research questions about individual differences and mechanisms of chronic insomnia.

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Author Contribution Statement

Alisa Huskey: Methodology, Investigation, Data Curation, Writing – Original Draft, Writing- Review & Editing, Supervision, Project Administration **Sarah E. Emert** Methodology, Investigation, Data Curation, Writing – Original Draft, Writing- Review & Editing, Supervision, Project Administration **Samantha M. Nagy** Investigation, Writing – Review & Editing, Supervision **Kelly Kim** Methodology, Software, Investigation, Data Curation, Writing – Review & Editing **Jaqueline Leete** Methodology, Investigation, Data Curation, Writing – Review & Editing **Nicole Lopez** Investigation, Data Curation, Writing – Original Draft, Writing- Review & Editing, Project Administration **Ethan Olson** Investigation, Data Curation, Writing – Original Draft, Writing- Review & Editing **William D.S. Killgore** Methodology, Resources **Matthew D. Grilli** Methodology, Supervision **Daniel J. Taylor** Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing- Review & Editing, Supervision, Funding Acquisition

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Conflict of Interest

Authors have no conflicts of interest to declare.

Ethics Statement

All participants signed an informed consent form prior to enrollment into the study. This study was approved by the university Institutional Review Board and monitored on an annual basis.

Data Availability Statement

Data availability is not applicable to this article as no new data were created or analysed in this study.

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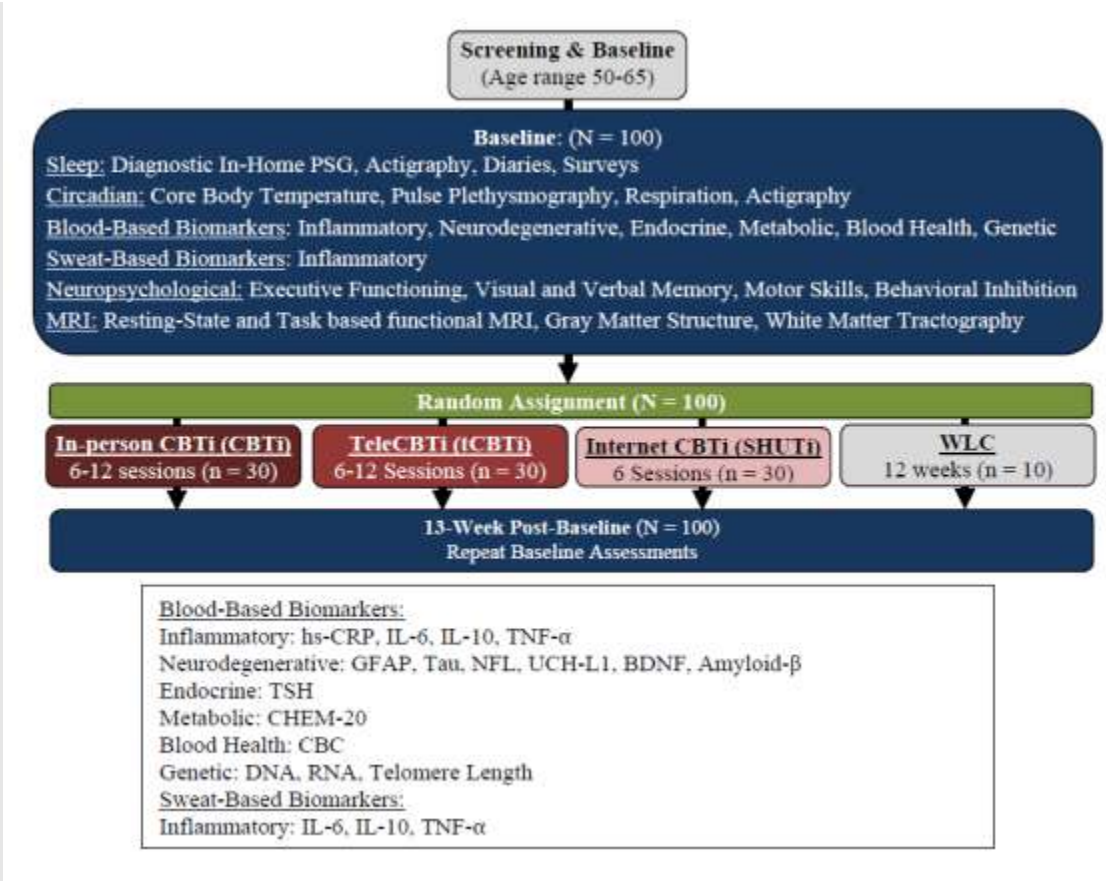

Figure 1. Detailed Design Flow

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Table 1

Schedule of measures at each assessment time-point.

Measures	Screening	Baseline	Intervention	Post-Treatment	Follow-Up
Consent					
1. Informed Consent	X				
Screening					
2. Online Demographics	X				
3. Eligibility Questions (i.e., age, location, equipment)	X				
4. Sleep Condition Indicator (SCI)	X				
5. MRI Safety Checklist	X	X			
Sleep Measures					
6. Insomnia Severity Index (ISI)		X	X	X	X
7. Insomnia Identity Item		X		X	X
8. Reduced Composite Scale of Morningness (rCSM)		X		X	X
9. Consensus Sleep Diary (CSD)*	X	X	X	X	
10. 1-week Actigraphy (Actiwatch Spectrum)		X		X	
11. In-home Ambulatory Polysomnography (PSG)		X		X	
12. Sleep Need Questionnaire (SNQ)*		X	X	X	X
13. PROMIS Sleep Related Impairment 8a*		X	X	X	X
14. Glasgow Sleep Effort Scale (GSES)*		X			X
15. Dysfunctional Beliefs about Sleep (DBAS)		X	X		X
16. Self-Assessment of Sleep Survey (SASS)		X		X	X
17. Multidimensional Fatigue Inventory (MFI)		X		X	X

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10. 1-week Actigraphy (Actiwatch Spectrum)		X		X	
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12. Sleep Need Questionnaire (SNQ)*		X	X	X	X
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14. Glasgow Sleep Effort Scale (GSES)*		X			X
15. Dysfunctional Beliefs about Sleep (DBAS)		X	X		X
16. Self-Assessment of Sleep Survey (SASS)		X		X	X
17. Multidimensional Fatigue Inventory (MFI)		X		X	X

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Clinical Interview					
18. Structured Clinical Interview for DSM-5 Sleep Disorders-Revised (SCISD-R)		X			
19. Montreal Cognitive Assessment (MoCA)		X			
20. Mini International Neuropsychiatric Interview (MINI)		X			
Circadian Measures					
21. Core Body Temperature [CBT]		X		X	
22. Electrocardiography (ECG)		X		X	
23. Respiration Rate		X		X	
24. Skin Temperature		X		X	
25. Movement (Actigraphy)		X		X	
Blood-Based Biomarkers					
26. Inflammatory: High Sensitivity C-reactive protein (hs-CRP), Interleukin (IL)-6, IL-10, Tumor necrosis factor alpha (TNF-α)		X		X	
27. Neurodegenerative: Glial fibrillary acidic protein (GFAP), Tau, Neurofilament Light Chain (NFL), Ubiquitin C-terminal hydrolase L1 (UCH-L1), Brain-derived neurotrophic factor (BDNF), Amyloid-β		X		X	
28. Endocrine: Thyroid Stimulating Hormone (TSH), High Sensitivity		X		X	
29. Metabolic: Chemistry Screen (CHEM-20)		X		X	
30. Blood Health: Complete Blood Count (CBC)		X		X	
31. Genetic: DNA, RNA, Telomere Length		X		X	

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Sweat-Based Biomarkers					
32. Inflammatory: Interleukin (IL)-6, IL-10, Tumor necrosis factor alpha (TNF-α)		X		X	
Cognitive/Neuropsychological					
33. Tablet-based Neurocognitive Assessment Tool (NIH EXAMINER)		X		X	
Magnetic Resonance Imaging					
34. Gray Matter Structure (T1-MPRAGE)		X		X	
35. Resting-State Functional MRI (fMRI)		X		X	
36. Multisource Interference Task (task-fMRI)		X		X	
37. White Matter Tractography (DTI)		X		X	
Self-Report Battery					
Health Measures:					
38. General Health Questionnaire		X		X	X
39. History of Head Injury Modified for Civilians		X		X	X
40. Patient Health Questionnaire-15 (PHQ-15)		X		X	X
Psychosocial Measures:					
41. Patient Health Questionnaire-9 (PHQ-9)		X		X	X
42. Generalized Anxiety Disorder (GAD-7)		X		X	X
43. Perceived Stress Scale (PSS-4)		X		X	X
44. Dimensions of Anger Reactions-5 (DAR-5)		X		X	X
45. Alcohol Use Disorders Identification Test (AUDIT)		X		X	X
46. Brief Inventory of Psychosocial Functioning (B-IPF)		X		X	X
47. Ten-Item Personality Inventory (TIPI)		X		X	X
48. Posttraumatic Stress Disorder Checklist (PCL-5)		X		X	X

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49. MacArthur Scale of Subjective Social Status		X			
50. Resting Online Technology Questions		X			
Therapy Process Measures					
51. Credibility and Expectancy Questionnaire (CEQ)			X		
52. Homework Compliance (Therapist Rated)			X		
53. Qualitative Interviews			X		
54. Fidelity Ratings			X		

*All participants complete 2 weeks of sleep diaries at baseline and post-treatment as well as a weekly survey battery for all 12 weeks, regardless of when treatment was concluded. Only participants enrolled in in-person or telehealth complete daily sleep diaries until the end of their individualized duration of treatment.

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