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Efficacy of cognitive behavioral therapy for insomnia and lemborexant medication for different subtypes of chronic insomnia: study protocol for a randomized controlled trial

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Abstract

Introduction Insomnia is a prevalent yet under-characterized disorder, particularly regarding the heterogeneity of patients and their associated responses to different treatment modalities. This often leads to suboptimal management. There is a need to consider personalized approaches tailored to the characteristics of insomnia phenotypes with regard to objective evidence of shortened sleep duration (< 6 h). This study will examine whether there is a differential treatment response to cognitive behavioral therapy for insomnia (CBT-I) versus pharmacotherapy (lemborexant) as a function of insomnia phenotypes (i.e., ± 6 h of sleep).

Methods This study is a three-arm pragmatic randomized clinical trial, which will enroll 90 adults with chronic insomnia disorder and anxiety/depressive symptoms. Eligible participants will be randomized to one of three conditions (1:1:1) involving CBT-I, lemborexant (Dual Orexin Receptor Antagonist) or placebo medication. Treatment outcomes will be assessed at post-treatment and 6-month follow-up. Insomnia symptom severity as measured by the Insomnia Severity Index will serve as the primary outcome for treatment comparisons. Secondary outcomes will include daily sleep/wake variables derived from the Consensus Sleep Diary, subjective measures of fatigue, mood, mental well-being, functional impairments, and sleep-related beliefs and attitudes. In addition, changes in cognitive performance will be examined as an exploratory outcome. Sleep reactivity and arousal level will be evaluated as potential mediators of treatment-related changes in CBT-I and pharmacotherapy.

Discussion This study will contribute to the development of personalized medicine for managing different insomnia phenotypes and will have implication for knowledge mobilization of sleep research.

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Keywords Insomnia phenotypes, Treatment, Cognitive behavioral therapy for insomnia, Pharmacotherapy

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Background

Insomnia disorder is a highly prevalent sleep disorder characterized by dissatisfaction with sleep duration or quality and associated with difficulty staying or maintaining sleep that causes significant distress or daytime impairments [1]. Recent population estimates suggested that approximately 16% of Canadian adults meet the criteria for an insomnia disorder [2]. Insomnia is associated with increased risk of mental disorders [3], medical problems [4] and accidents [5], as well as reduced quality of life and productivity [6, 7], leading to increased healthcare utilization and costs [8, 9]. Despite its high prevalence, adverse impact, economic burden, and heterogeneous clinical presentations, insomnia remains an under-characterized condition, especially regarding the unique clinical presentations of individual patients and their associated responses to different treatment modalities, which can lead to suboptimal management. Thus, it is important to match treatment modalities to the characteristics of heterogeneous insomnia subtypes.

Treatment options for insomnia

Current treatment options for insomnia recommended in clinical practice guidelines include two major approaches: psychological and behavioral therapies (such as cognitive behavioral therapy for insomnia [CBT-I]) and medications [10–12].

CBT-I is a multicomponent treatment that aims at altering the behavioral practices (e.g., staying in bed while unable to sleep) and psychological factors (e.g., unhelpful sleep beliefs) that contribute to insomnia [13]. The core components of CBT-I are behavioral strategies (i.e., sleep restriction and stimulus control procedures), relaxation training, psychological and cognitive interventions targeted at the perpetuating factors of insomnia. Currently, CBT-I is widely recognized as the first-line treatment for chronic insomnia [10, 11], with sufficient scientific evidence supporting its efficacy. Previous meta-analysis suggests moderate to large effects of CBT-I on improving insomnia symptom severity (Hedges' g= 0.98; 95% confidence interval [CI], 0.82 to 1.15), sleep efficiency (g =0.71; 95% CI, 0.61 to 82), sleep-onset latency (g =0.57; 95% CI, 0.50 to 0.65), and time awake after sleep onset (g =0.63; 95% CI, 0.53 to 0.73) [14]. The clinically significant effects produced by CBT-I have been found to be sustained for up to one year after therapy, albeit a decline over time [15].

Despite the clinical gains that people with insomnia experience with CBT-I, a sizable proportion of treated individuals still respond insufficiently, with about 50% not achieving full remission after treatment [13]. The non-remission rates are even higher (up to 64%) in patients with comorbid psychiatric and medical conditions [16], indicating that patient characteristics related to the heterogeneity of treatment responses should be investigated and taken into account to better determine the preferential treatment for insomnia patients.

The use of hypnotic medications has been advised to treat insomnia when CBT-I is not available or ineffective [11]. Currently, a significant portion of hypnotic medications approved by Food and Drug Administration (FDA) are benzodiazepine receptor agonists (BZRAs), including both benzodiazepines and nonbenzodiazepines (also known as Z-drugs). BZRAs exert their effects via benzodiazepine receptors by enhancing the action of the inhibitory neurotransmitter γ-aminobutyric acid (GABA), thereby leading to sleep promotion. Based on the findings of a recent network meta-analysis, benzodiazepines were effective in the acute treatment of insomnia, whereas their tolerability and safety profiles were not favorable, and there is limited data regarding long-term use [17]. On the other hand, Z-drugs, especially eszopiclone, may be a better choice in terms of long-term use and acceptability; however, the risks of substantial adverse events (e.g., falls) often preclude their use [17]. Because of these safety concerns, the America Geriatrics Society recommend avoiding both benzodiazepines and Z-drugs in older adults (Beers criteria) [18].

As more recently developed and approved hypnotic medications, Dual Orexin Receptor Antagonists (DORAs) provide an alternative to existing pharmacological treatments for insomnia. Their presumed mechanism of action is through blocking of orexin receptors 1 and 2, which inhibit arousal and wakefulness modulated by orexin neuropeptides. Lemborexant (Dayvigo) is one of the DORAs approved by FDA and Health Canada for the treatment of adult with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. Current evidence indicates that lemborexant is an efficacious agent for improving sleep continuity and duration with effects maintained up to one year [19], and it may also increase REM sleep and slow wave sleep [20, 21]. In addition, it has been found to be more efficacious than placebo in both short-term (Cohen's d= 0.36; 95% CI, 0.08 to 0.63) and long-term treatment (d =0.41; 95% CI, 0.04 to 0.78) [17]. Notably, lemborexant produces less cognitive and psychomotor impairment than BZRAs [22], indicating that it may be a more appropriate pharmacological treatment option for individuals who do not respond adequately to CBT-I.

Sleep duration phenotype and implications for tailored treatment

As suggested by previous studies, there are potentially several insomnia phenotypes, with one particular phenotype based on objective sleep duration: insomnia

disorder with short objective sleep duration (< 6 h) and those without objective short sleep duration (≥ 6 h) [23]. Insomnia with objective short sleep duration is believed to be biologically rooted, as evidenced by increased arousal (e.g., hyperactivity of the hypothalamic–pituitary–adrenal [HPA] axis and increased cortisol), increased risk of medical morbidity (e.g., hypertension and reduced heart rate variability) [24] and cognitive difficulties [25–30]. Cortisol is a particularly important biological marker for objective short sleep duration [31]. However, this is not intended to create a false dichotomy between psychological and biological variables, as they are interrelated. Rather, biological markers help differentiate patients with short sleep duration from those with normal or near-normal sleep duration and may also help explain the inadequate response to CBT-I (i.e., lower remission rates after CBT-I) observed in insomnia patients with short sleep duration [32]. For patients with short sleep duration, a biological approach (i.e., medication) might be a more suitable treatment [23].

In contrast, insomnia disorder with normal or near-normal sleep duration (i.e., 6 h or more) is less strongly associated with physiological arousal and medical morbidity. Instead, the profiles of patients with normal or near-normal sleep duration are more consistent with depressed and anxious mood, as well as rumination [25]. These patients often show elevated depressive and anxiety symptoms, increased worry about falling asleep and greater distress about daytime functioning (e.g., fatigue) [27, 33–35], which can be effectively addressed by CBT-I intervention [36, 37]. As for patients with short sleep duration, they may also exhibit mood symptoms and fatigue, albeit to a lesser degree, given the overlap between the two phenotypes in terms of their close association with mental health problems [23]. Therefore, CBT-I may still have value in addressing the mood symptoms of objective short sleepers, even though they experience less sleep improvement with this treatment, which warrants further investigation.

Objectives

The main objective of this study is to contrast the effectiveness of CBT-I and pharmacotherapy (lemborexant) compared to placebo on sleep and mental health outcomes in people with insomnia disorder and anxiety/depressive symptoms. In addition, the study will evaluate whether insomnia phenotypes (i.e., ±6 h of sleep) at baseline moderate the effectiveness of the two types of interventions on both sleep and mental health outcomes.

Methods and analysis

Study design and participants

This study is a three-arm pragmatic randomized clinical trial. Ninety adults (18 years of age or older) will be recruited from the community at three Canadian sites (Québec City, Toronto, Ottawa; 30 participants per site) through referrals by family physicians, advertisement in newspapers, on the radio, and in social media. The inclusion and exclusion criteria are presented in Table 1. The criteria are set broadly to allow the enrollment of a widely representative sample of people with insomnia and common comorbidities typically seen in clinical practice. Individuals with a comorbid medical or psychiatric condition will be excluded only if the co-existing condition is life-threatening, untreated, or would be a contra-indication to using the study medications.

Individuals using sleep aids (prescribed or over-the-counter) will be included if they are willing and able to

Table 1 Eligibility criteria

Inclusion criteria

1) 18 years of age or older at the time of enrollment
2) Meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for insomnia disorder (Duke Sleep Interview), with total Insomnia Severity Index (ISI) score > 10, and score ≥ 2 on either the interference or distress item
3) Minimal symptoms of anxiety and/or depression with Patient Health Questionnaire (PHQ-9) > 4 and/or Generalized Anxiety Disorder (GAD-7) > 4
4) Ability to read and understand French or English
5) Ability to use a smartphone, tablet, or computer, and access to home internet connection

Exclusion criteria

1) Presence of a lifetime diagnosis of any psychotic or bipolar disorder
2) Untreated psychiatric disorder (e.g., major depression) or risk for suicide
3) Substance/alcohol use disorder within the past year
4) Any life-threatening or progressive medical illness (e.g., cancer, chronic obstructive pulmonary disease) or neurological degenerative disease (e.g., dementia)
5) Current use of sleep-promoting medications (prescribed or over-the-counter) or cannabis-derived products for sleep more than two nights per week
6) Current use of tricyclic antidepressants, monoamine oxidase inhibitors, or atypical antidepressants
7) Reported diagnosis of sleep disorder other than insomnia (e.g., obstructive sleep apnea, restless legs syndrome, rapid eye movement behavior disorder, delayed phase sleep disorder, narcolepsy)
8) Total score > 5 on the Stop-Bang Questionnaire and/or clinical symptoms suggestive of sleep apnea (excessive daytime sleepiness), or Epworth Sleepiness Scale (ESS) score > 10, restless legs syndrome or other signs of other sleep disorders
9) Atypical sleep schedules (i.e., habitual bedtimes later than 2:00 AM and rising times later than 10:00 AM on more than two days/nights per week as documented from a sleep diary)
10) Working night shifts more than five nights per month in the last six months
11) Consuming 2 or more alcoholic beverages per day regularly (3 days or more per week)
12) Any contra-indications to using the study medication, including lung disease/breathing problems (e.g., chronic obstructive pulmonary disease), use of strong or moderate CYP3A inducers (strong—rifampin, carbamazepine, and St. John's Wort) (moderate—bosentan, efavirenz, etravirine, and modafinil), pregnant and breastfeeding women
13) Not using any method of birth control

discontinue its use at least two weeks before baseline assessment. Participants using alcohol as a sleep aid or consuming alcohol after 7:00 PM on a regular basis will be required to discontinue this practice at least two weeks prior to baseline assessment. Those using alcohol occasionally (5 or fewer drinks per week) will be informed not to use alcohol with the study medications as it may potentiate its impact. Individuals on stable dosages (for at least two months) of certain psychotropic medications (e.g., anxiolytics, antidepressants, except those listed in exclusion criteria 6) will not be automatically excluded from the study. Those on stable dosages (for at least two months) and who show at least partial remission from their mood or anxiety disorder as assessed by Mini-International Neuropsychiatric Interview (MINI) [38] will be accepted in the study if they meet the selection criteria above.

Eligible Participants (n = 90) will be randomized to one of three conditions (1:1:1) involving a 8-week treatment protocol (6 consultations over an 8-week period): 1) CBT-I (n = 30), 2) an active hypnotic medication (lemborexant, n = 30) or 3) a placebo medication (n = 30), stratified by objective (EEG-defined) sleep duration (< 6 h vs. ≥ 6 h) and age (< 50 years old vs. ≥ 50 years old). Randomization will be based on a computer-generated list of numbers for each site which will be created by a statistician and the participants' allocation will be concealed by using sequentially numbered sealed envelopes that are opened by study coordinators only after a patient meets all selection criteria and is ready to initiate treatment.

The study protocol has been approved by the ethics committees at the three main sites: the Research Ethics Board, Institut universitaire en santé mentale de Québec, Québec, Canada, Toronto Metropolitan University Research Ethics Board, Toronto, Ontario, and the Royal Ottawa Health Care Group (ROHCG) Research Ethics Board, Ottawa, Ontario. All important protocol modifications will be communicated to ethics committees. Study coordinators will obtain written informed consent from all prospective participants at baseline. The study recruitment started on April 1, 2025, and is expected to be completed by December 31, 2026.

Procedures

Figure 1 depicts the study timeline. Potential candidates will be contacted by phone and invited to provide verbal consent for the phone screening process. Those who seem eligible and interested at the end of the telephone screening will be invited for an in-person evaluation. During this visit, they will sign the consent form to enroll in the study and complete different evaluations to determine their eligibility for randomization: medical history, brief physical exam, MINI interview, sleep/insomnia, anxiety, depressive symptoms questionnaires (see Table 2 for details). They will then receive actigraphy (G3X) and EEG headband (Muse-S, Interaxon) with instructions for 7 days of home-based sleep monitoring. After completing baseline assessment, participants meeting the criteria will be randomized to receive one of the three treatments. Outcome measures will be assessed at the end of the treatment (weeks 9–10) and 6 months after the post-treatment assessment. One-week ambulatory monitoring (EEG headband and actigraphy) will be conducted only at baseline and post-treatment assessment. Treatment unblinding will be conducted by the study coordinator at each site after completion of the post-treatment assessment. Participants in the lemborexant and placebo control arms will be offered the option to receive CBT-I after completion of the follow-up measures.

Treatments

CBT-I and medication treatment will be administered in the context of six individual, in-person or online consultations, conducted over an 8-week period. Therapists will use treatment manuals developed for this project to standardize the delivery of both treatments across participants and sites, and to minimize overlap between the two therapeutic approaches. Therapy sessions will occur at each of the three study sites: Centre d'étude des troubles du sommeil (Centre de recherche CERVO) at Laval University in Québec, Sleep and Depression Laboratory at Toronto Metropolitan University in Toronto and the University of Ottawa Institute of Mental Health Research at The Royal Hospital.

Cognitive Behavioral Treatment for Insomnia (CBT-I)

Participants in this treatment group will receive CBT-I [39]. CBT-I sessions, which include an overview of insomnia, sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relapse prevention, will occur weekly for the first 4 sessions and biweekly for the last 2 sessions (treatment phase is thus 8 weeks). Graduate level students in clinical psychology will serve as therapists for this project. Therapists will receive training from licensed psychologists with extensive experience in conducting CBT-I and will be provided with a treatment manual.

Medication

Participants assigned to the medication groups (active and placebo) will be prescribed 5 to 10 mg of lemborexant or placebo to be taken at bedtime in 5 mg identical capsules. Lemborexant (Dayvigo) is approved by Health Canada for the treatment of insomnia. The choice of lemborexant as the active medication was based on the existing evidence of its efficacy for improving insomnia symptoms in both

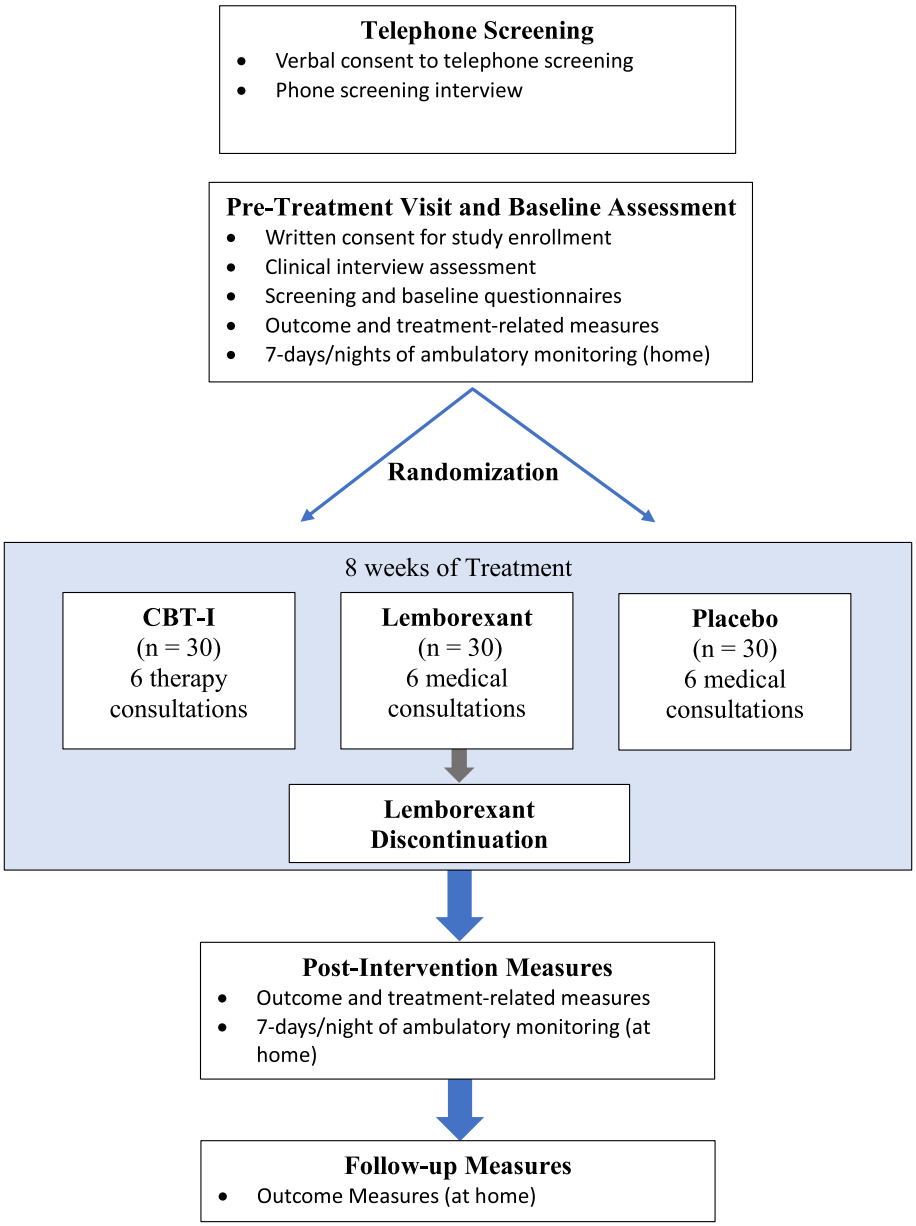

Fig. 1 Study timeline

short-term and long-term treatment [17, 19–21]. In addition, rather than inhibiting the central nervous system, lemborexant exerts its effects by temporarily blocking the orexin pathway, which results in less cognitive and psychomotor impairment than BZRAs [22].

Both prescribing physicians and participants will be blind to treatment. Medication will be prescribed and monitored by the study physician and dispensed by the research pharmacy at each study site. Pharmacy staff will package medications for each participant in a generic bottle labeled with the participant's ID code and treatment dates (identical for the lemborexant and placebo arms). Six consultation visits will be conducted during the 8-week treatment phase to monitor treatment response and drug side effects. The starting dose will be 5 mg with titration to 10 mg if needed (i.e., based on clinical response and tolerability) following the first week. During each consultation, the study physician will document prescribed dosage on the dosage form, which will contain participant ID code, consult date, prescribed dosages, and notes about any deviation from prescribed dosage. Unused medication will be returned to the study

Table 2 Time Course of Study Measures

	Screening/ Eligibility (- 4 weeks)	Baseline (— 2 weeks)	Six consultations over an 8-week treatment period Weeks 0–8	Post-Treatment 2 weeks Weeks 9–10	Follow-Up 6-month Weeks 26–27 after end of treatment
Screening Measures (Demographics, health, sleep disorders)					
Sociodemographics, medical and medications checklist,	X				
Duke Sleep Interview	X				
Mini-International Neuropsychiatric Interview, STOP-Bang, International Restless Legs Questionnaire, Epworth Sleepiness Scale	X				
EEG (7 nights), actigraphy (7 days and nights)		X		X	
Outcome Measures (Sleep, insomnia, daytime symptoms, burden)					
Consensus sleep diary	X	X	X	X	X
Insomnia Severity Index	X	X	X	X	X
Patient Health Questionnaire-9	X	X		X	X
Generalized Anxiety Disorder 7-item	X	X		X	X
Dysfunctional Beliefs and Attitudes about Sleep		X		X	X
Fatigue Severity Scale		X		X	X
Work and Social Impairment Scale		X		X	X
WHO-5 Well-Being Index		X		X	X
Cognitive Failures Questionnaire 2.0		X		X	
Treatment-Related Measures					
Treatment acceptability and satisfaction		X		X	X
Treatment adherence scale			X		
Ford Insomnia Response to Stress Test, Arousal Predisposition Scale, Pre-Sleep Arousal Scale	X		X	X	
Adverse Events (Systematic Assessment for Treatment Emergent Events)		X	X	X	

physician/pharmacy at each consultation visit. Physicians and participants will agree upon the specific dose to maximize positive effects on insomnia and minimize side effects. Both the placebo and lemborexant pills will be encapsulated to be visually identical. For participants who would elect telehealth/virtual rather than in-person consultations, their medication supply will be sent by local ground transportation (e.g., medical courier).

Measures

Screening instruments

Structured clinical interviews will be used to screen potential participants. The Duke Structured Interview for Sleep Disorders (DSISD) [40] will be administered to ascertain that participants meet criteria for an insomnia disorder and to rule out other sleep disorders such as obstructive sleep apnea, restless legs syndrome, REM behavior disorder, etc. Psychiatric evaluation using the MINI will be conducted to determine the presence of psychiatric disorders that could lead to exclusion, as well as to characterize the sample. All interviews are audiotaped, and reliability checks are conducted on 15% of them. The STOP-Bang [41], the International Restless Legs Questionnaire (IRLSQ) [42] and the Epworth Sleepiness Scale (ESS) [43] will be administered to exclude participants with obstructive sleep apnea, restless legs syndrome, and excessive sleepiness, respectively (see Table 2 for details).

Outcome measures

The primary outcome is insomnia symptoms severity as measured by the Insomnia Severity Index (ISI) [44] at post-treatment. An ISI score <8 will be used to define remission. Treatment response will be defined at each assessment as a reduction of 8 points or more on the ISI compared with the baseline score. The ISI is a self-report questionnaire evaluating seven dimensions of insomnia—severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties. Each item is rated on a 0 to 4 scale and the total score ranges from 0 to 28.

Several secondary outcomes will also be monitored, including daily sleep/wake variables, mood symptoms, daytime functions, and sleep-related beliefs and attitudes. Sleep/wake variables will include sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE) derived from the from the Consensus Sleep Diary [45]. Treatment-related changes in mood symptoms and mental well-being will be assessed with Patient Health Questionnaire-9 (PHQ-9) [46], Generalized Anxiety Disorder 7-item (GAD-7) [47], and World Health Organization Well-Being Index (WHO-5) [48]. The PHQ-9 is a questionnaire of 9 items to assess the presence of symptoms of depression. The GAD-7 is a 7-item scale evaluating anxiety severity in the last two weeks. Changes in daytime functions will be evaluated by Fatigue Severity Scale (FSS) [49] and Work and Social Adjustment Scale (WSAS) [50]. The FSS is a 9-item scale measuring fatigue severity and how it interferes with everyday life. The WSAS assesses the functional impact of a specific disorder (in our study, insomnia) on five domains: ability to work, home management, social leisure activities, private leisure activities, and relationships. Changes in sleep-related beliefs and attitudes will be assessed using the Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16) [51]. Changes in cognitive performance measured by Cognitive Failures Questionnaire 2.0 (CFQ 2.0) [52] will serve as an exploratory outcome. The CFQ 2.0 is a 15-item questionnaire asking respondents to rate the frequency with which they make minor mistakes (e.g., forgetting to take their keys, calling people by the wrong name).

Home-based monitoring

Participants will undergo 7 days of home-based sleep monitoring (EEG headband [Muse-S, Interaxon]) at baseline and post-treatment. During the same period, ambulatory monitoring with a wrist-worn actigraph (G3X) will be used continuously across the 24-h cycle. On the last evening of each ambulatory monitoring period, a 5-min resting-state recording will measure pre/post-sleep cortical and autonomic arousal: i) 30 min before sleep on the evening of the seventh day, and ii) 30 min after waking up on the following morning. Data from home-based monitoring will be used as measures to define insomnia phenotypes (i.e., objective sleep duration and cortisol level).

The EEG headband counts 5 dry electrodes (AF7, AF8, FPZ, T9, T10) and a heart rate sensor embedded in a soft cloth wireless headband. Anonymous data from the Muse-S device are live streamed via Bluetooth to adjacent iOS or android devices (i.e., smartphone, tablet or iPad).

Participants will attend a training session on how to use these devices. They will also be provided with an instruction video (French: https://youtu.be/FR2Ou94dwJs—English: https://youtu.be/TxYYGwCj2t4) and written guidelines. Data quality will be monitored remotely across the study and additional training will be provided as needed.

On the last day of the ambulatory monitoring week, saliva samples for cortisol will be collected to assess activity of the HPA axis. Using our home-based protocol, participants will be provided with seven tubes to collect saliva samples at the following times: upon awakening; 15, 30, 45 and 60 min after awakening; as well as 4 h and 5 min before habitual bedtime. All study materials will be brought back to the laboratory at the end of the monitoring week. Samples can be stored at room temperature up to 24 h during collection period, then collected by staff and stored at − 20 degree Celsius until time of assay. After being centrifuged, saliva samples will be frozen for at least 2 weeks before being processed. All saliva samples will be assayed for cortisol by enzyme immunoassay kits (EIA, Alpo, Salem, NH).

Treatment-related measures

Sleep reactivity (Ford Insomnia Response to Stress Test [FIRST]) [53], predisposition to arousal (Arousal Predisposition Scale [APS]) [54], and pre-sleep arousal (Pre-Sleep Arousal Scale [PSAS]) [55] will be evaluated as potential mediators of treatment effects. Sleep reactivity and increased arousal have been considered as heterogeneous aetiological factors underlying insomnia [24, 56], with insomnia disorder with objective short sleep duration being associated with higher levels of sleep reactivity and arousal than those with normal or near-normal sleep duration. Therefore, the changes in sleep reactivity and arousal may play an important role in mediating responses to psychological and medication therapies across different insomnia phenotypes.

Treatment adherence will be monitored throughout the treatment period using the Treatment Adherence Scale. An amended version of the Therapy Evaluation Questionnaire [57], specifically adapted for the current study, will be used to assess treatment credibility, acceptability, and patient satisfaction.

Adverse events and serious adverse events will be monitored for participants in the lemborexant and placebo intervention arms using the Systematic Assessment for Treatment Emergent Events (SAFTEE), a reliable and valid instrument for assessing AEs that may or may not be related to the study treatments [58]. AEs and SAEs will be assessed at each visit during the 8 weeks of the treatment as well as two weeks after the end of the treatment. The study physician and the PI will decide whether the participant should be withdrawn from study or in the case of SAEs, whether the study should be discontinued.

Data management and statistical analyses

Data management

Regular monitoring will be conducted to ensure (1) data collected are consistent with the protocol (2) no key data are missing and (3) data appears to be valid (range checks, calendar checks and checking the variability of repeated measures). Each site will send data to the lead site (Université Laval) using agreed upon secure methods. Case report forms will be entered via the data management system using a web-based REDCap (Research Electronic Data Capture) data entry system. Physiological (EEG and saliva) and actigraphy data will be sent to the Sleep Research Unit of the University of Ottawa via the cloud secure portion of the researcher portal. The electronic database containing the anonymous physiological and questionnaires data will be stored on protected servers with password-protected restricted access. An anonymous main database containing research identification codes, the name and contact details of the main care provider(s) identified by each participant as the first contact point, individual study timelines, and research notes will be kept on a password-protected server at the site where the participant was recruited. Except for the recruitment list, consent database, and master code list, all data will be identified exclusively by an anonymous identification code. All co-investigators and their assistants will have access to the anonymous data for analysis purposes. Sharing of data outside of the listed study team, such as through collaboration will be arranged only after express agreement of the PI through a data sharing agreement.

Statistical analyses

The sleep diary, actigraphy, and EEG headband data will be presented as nightly means averaged over the 2-week period (for the diary data) or 1-week (for the actigraphy and EEG headband data) period for each assessment. Other measures will consist of one global score each from the self-reported scales, such as the ISI.

Data will be analyzed with an intent-to-treat approach. All participants with at least one observation post-randomization will be included in the analyses. Preliminary analyses of variance (ANOVAs) and chi-squared tests will be conducted on selected demographic (e.g., age, sex/gender, level of education) and clinical variables (e.g., insomnia severity, presence of comorbid depression/anxiety, prior use of hypnotic medications) to ensure comparability of the three groups at baseline. Variables with significant between-group differences will be examined to check whether they should be included as covariates in subsequent analyses. To examine changes with treatment (i.e., baseline to post-treatment), mixed models will be used. Follow-up data will also be analyzed with mixed models comparing post-treatment data with the one of the 6-month follow-up. Statistical analyses will be completed with SAS version 9.4.

The dependent variables will be grouped into four groups: (a) sleep/insomnia measures: insomnia severity (ISI) and responders/remitters analyses, and sleep continuity (i.e., CSD sleep onset latency, time awake after sleep onset, total sleep time); (b) daytime functioning measures: fatigue (FSS), work/social adjustment (WSAS) and cognitive performance (CFQ 2.0); (c) psychological measures: depression (PHQ-9), anxiety (GAD-7), and well-being (WHO-5); (d) mechanism/process measures: behavioral (i.e., time spent in bed) and cognitive (i.e., worry, DBAS-16) processes, and potential mediators (i.e., FIRST, APS, PSAS).

Using multilevel longitudinal linear analyses and controlling for site and patient clustering, we will examine time, group and interaction effects on insomnia outcomes, i.e., insomnia symptom severity, remission (ISI score <8) and response rates (ISI change score >8) [44] and mean subjective sleep duration and sleep continuity from CSD data. Similar analyses will be conducted on other secondary and exploratory measures including mood symptoms (PHQ-9 and GAD-7), mental well-being (WHO-5), daytime functions (FSS and WSAS), sleep-related beliefs and attitudes (DBAS-16) and cognitive performance (CFQ 2.0). Subgroup analyses will examine the effects of demographic factors in aggregated and disaggregated form (e.g., age, sex, gender, race and socioeconomic status. It is expected that participants with insomnia and normal or near-normal sleep duration and who receive CBT-I will have better treatment response and remission rates, greater improvements on CSD sleep measures, and greater improvements on measures of anxiety, depression and fatigue compared to those with short sleep duration (< 6 h; biological phenotype). Those with insomnia and short sleep duration are expected to have a better treatment response and remission rates with medication than CBT-I, and greater improvements on objective sleep duration. Improvements on depression, anxiety, and fatigue are expected to be significantly lower in the medication relative to the CBT-I group. Both treatment groups will show greater improvements on all outcomes than the control group. Only the short sleep subgroup should show decreased post-treatment salivary cortisol concentrations.

Primary outcomes analyses Question 1. Which treatment (CBT-I and pharmacotherapy) is more effective at improving sleep outcomes in people with insomnia disorder and anxiety/depressive symptoms? The first question will be examined by comparing changes between treatment conditions (i.e., CBT-I vs. pharmacotherapy vs.

placebo) on the sleep/insomnia measures from baseline (Time 1) to the end of treatment (Time 2). A factorial 3 (Groups) X 2 (Times) split-plot mixed model analysis will be completed to test group, time, and interaction effects. Significant group X time interactions will be decomposed using simple main effects in order to compare pre to post changes associated with each treatment condition. Follow-up data for the CBT-I and medication conditions will be analyzed to examine whether group differences in improvement are maintained over time (Time 3).

Question 2. Which treatment (CBT-I and pharmacotherapy) is more effective at improving mental health outcomes in people with insomnia disorder and anxiety/depressive symptoms? The second question will be examined by comparing changes between treatment conditions (i.e., CBT-I vs. pharmacotherapy vs. placebo) on mental health measures from baseline (Time 1) to the end of treatment (Time 2). The same data analytic plan from question 1 will be implemented for this question. Follow-up data (Time 3) will be analyzed to examine whether changes at post-treatment are maintained over time.

Secondary outcomes analyses Question 3. Do insomnia phenotypes (i.e., ±6 h of sleep) at baseline affect the effectiveness of the interventions on both sleep and mental health outcomes? The third question will examine if the effectiveness of CBT-I and pharmacotherapy varies in adults sleeping less or more than 6 h/night at the end of treatment (Time 2). The same data analytic plan from questions 1 and 2 will be implemented for this question, except that participants will be divided into two groups: insomnia with short sleep duration (< 6 h) and insomnia with normal or near-normal sleep duration (≥ 6 h). The effectiveness will be examined separately for sleep and mental health outcomes. Follow-up data (Time 3) for the CBT-I and pharmacotherapy conditions will be analyzed to examine whether the results are maintained over time. The level of significance will be set at 0.017 for sleep outcomes and for mental health outcomes.

Exploratory outcomes analyses Question 4. Which mechanisms of action are underlying the therapeutic response to both treatments (CBT-I and pharmacotherapy)? The fourth question will examine the mediators of change in CBT-I and pharmacotherapy from baseline (Time 1) to the end of treatment (Time 2). The potential mediators (sleep reactivity [FIRST] and arousal level [APS, PSAS]) will be evaluated between the 3rd-4th and after 6th therapy sessions. A two-step methodology will be used. Mixed models will be first completed to obtain the total time effect before the introduction of process variables as covariates. The direct time effect will be obtained after the introduction of covariates. Indirect time effect (i.e., the mediator effect) will be computed for each process and compared between treatment conditions.

Clinical significance In addition to statistical significance, we will examine the clinical significance of outcomes. Clinical significance will be examined by determining the proportion of individuals in each group reaching normative status on selected key variables at post-treatment and at the 6-month follow up, such as treatment responders and remitters defined according to the ISI score.

Power analysis For the primary sleep outcomes, data from a previous study in our lab were retrieved to estimate expected effect sizes [59]. Based on comparisons of pre to post changes, participants receiving CBT-I are expected to report larger reduction of insomnia symptom severity measured by ISI (Cohen's d ranging from 0.31 to 0.48, $M = 0.39$) compared to those using lemborexant. Using standard power conditions (alpha = 5% two-tailed, power = 80%) and assuming a 15% attrition rate, an averaged sample size of 29 participants per condition ($n = 87$ for the trial) would be sufficient to detect the smallest ES for this hypothesis, according to computations with G*Power 3.1.9 software. For the secondary sleep outcomes, data from another study in our lab [60] revealed that short sleepers expect to report larger pre to post reduction of sleep difficulties after CBT-I (Cohen's d ranging from 0.52 to 1.28, $M = 0.98$) compared to sleepers without objective short sleep duration. Using same power conditions, an averaged sample size of 15 participants per condition ($n = 45$ for the trial) appears sufficient to detect the smallest ES for this hypothesis. From both sets of questions, a final sample size of $n = 90$ is proposed for this trial.

Discussion

This study capitalizes on research opportunities for transforming medicine and public health outlined in the 2021 National Institutes of Health Sleep Research Plan [61]. As stated in the plan, identifying indicators of responses to therapeutic interventions is critical for translating advances in sleep science into medical and public health applications. In line with this notion, the current study will directly test whether psychological and biological profiles of insomnia are indicators for differential responses to psychological and medication therapies.

Currently, little is known about how to determine the optimal treatment for individual insomnia patients

based on the heterogeneity of insomnia sleep duration phenotypes (i.e., ±6 h of sleep). These two phenotypes are associated with distinct psychological and biological features, which may result in differential responses to insomnia treatment [23, 32, 62]. Given the biological profiles of objective short sleepers and their suboptimal response to CBT-I [62, 63], a biological treatment such as lemborexant medication may be a more suitable treatment for them. However, there are no data regarding the relative efficacy of CBT-I and lemborexant for managing insomnia, particularly in terms of how the efficacy of these treatments is moderated by insomnia phenotypes. Furthermore, there are no studies investigating the value of CBT-I in improving mental health across the two phenotypes.

The current study is designed to address these knowledge gaps in the insomnia treatment research, which includes following innovative features: 1) enrollment of representative sample of patients with insomnia disorder and anxiety/depressive symptoms typically seen in clinical practice; 2) the choice of lemborexant as a medication therapy, which has a favorable profile than BZRAs in terms of side effects [22]; and 3) use of a three-arm trial design that allows for direct comparisons between two different active treatments (i.e., CBT-I vs lemborexant) while controlling for the placebo effect.

Given the high prevalence, adverse impact, and economic burden of insomnia, the results of the current study are expected to have heuristic value for advancing the management of insomnia by informing clinical practice on how to match treatment modalities to the unique clinical presentations of patients with insomnia. This study could: 1) provide relevant and novel evidence that lays groundwork for personalized sleep medicine approaches, and 2) contribute to the knowledge mobilization of sleep research.

Abbreviations

ANOVAs	Analyses of variance
APS	Arousal Predisposition Scale
BZRAs	Benzodiazepine receptor agonists
CBT-I	Cognitive behavioral therapy for insomnia
CFQ	Cognitive Failures Questionnaire
DBAS	Dysfunctional Beliefs and Attitudes about Sleep
DORAs	Dual Orexin Receptor Antagonists
DSISD	Duke Structured Interview for Sleep Disorders
DSM- 5	Diagnostic and Statistical Manual of Mental Disorders
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FIRST	Ford Insomnia Response to Stress Test
FSS	Fatigue Severity Scale
GABA	γ-Aminobutyric acid
GAD- 7	Generalized Anxiety Disorder 7-item
HPA	Hypothalamic–pituitary–adrenal
IRLSQ	International Restless Legs Questionnaire
ISI	Insomnia Severity Index
MINI	Mini-International Neuropsychiatric Interview
PHQ- 9	Patient Health Questionnaire-9
PSAS	Pre-Sleep Arousal Scale
SAFTEE	Systematic Assessment for Treatment Emergent Events
SE	Sleep efficiency
SOL	Sleep onset latency
WASO	Wake time after sleep onset
WHO- 5	World Health Organization Well-Being Index
WSAS	Work and Social Adjustment Scale

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Authors' contributions

CMM is the sponsor with overall scientific responsibility for the study. SJC and CMM drafted the study protocol. CMM, CEC and RR conceived the study idea and supervised the project. CMM, HI, TTDV, CMS, CEC and RR contributed to the study methodology. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The manuscript is based on trial protocol version 2, which was issued on 11 November 2024. The study protocol has been approved by the ethics committees at the three main sites: the Research Ethics Board, Institut universitaire en santé mentale de Québec, Québec, Canada, Toronto Metropolitan University Research Ethics Board, Toronto, Ontario, and the Royal Ottawa Health Care Group (ROHCG) Research Ethics Board, Ottawa, Ontario. Study coordinators will obtain written informed consent from all prospective participants at baseline.

Consent for publication

All authors have given their consent for publication.

Competing interests

Dr. Morin reports receiving research grants from CIHR, NIH, Eisai, Idorsia, and Lallemand Health; serving on advisory boards for Eisai, Idorsia, and Haleon; and receiving royalties from Mapi Research Trust. Dr. Dang-Vu reports receiving research grants from CIHR, NSERC, Weston Family Foundation, Hypersomnia Foundation, Jazz Pharmaceuticals, and Paladin Labs; consulting fees from Eisai, Idorsia, and Jazz Pharmaceuticals; honoraria from Eisai and Jazz Pharmaceuticals; and serving on advisory boards for Eisai, Idorsia, and Hypersomnia Foundation. Dr. Robillard reports receiving research grants from CIHR, VAC, University of Ottawa Medical Research Funds, Ontario Early Researcher Awards, and Atlas institute for veterans and families; payment from Wellcome Foundation and Boehringer Ingelheim; serving as CO-Chair for Canadian Sleep Research Consortium and executive member for Canadian Sleep Society; and receiving In-Kind Contribution (EEG monitors) from Interaxon. The other co-authors declare that they have no competing interests.

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