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Protocol Title:	Treating Insomnia and Improving Metabolic Health in Midlife Women With Insomnia
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Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title:	Treating insomnia and improving metabolic health in midlife women with insomnia
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1. Background and Significance

A. Historical Background and Rationale

Insomnia is highly prevalent in women during midlife, particularly across the menopause transition, when epidemiologic studies show that *one-quarter of women meet criteria for chronic insomnia*.[1] Nocturnal hot flashes are the primary predictor of subjective sleep disturbance[2,3] and of a chronic insomnia syndrome in midlife women.[1] Hot flashes are the most common symptom of the menopause transition, occurring in up to three-quarters of women.[4] While present both during the day and night, nocturnal hot flashes (or night sweats) can be especially distressing when they disrupt sleep,[5] leading many women to seek medical treatment. By repeatedly awakening women, hot flashes are responsible for a sleep maintenance condition, which is the most common pattern of sleep disruption reported by midlife women.[6] We have shown that nocturnal hot flashes fragment sleep and increase the amount of time spent awake after sleep onset (WASO) on subjective (sleep diary) measures,[7] polysomnography,[7] and actigraphy. In contrast, hot flashes do not increase sleep-onset latency (SOL).[2,3,7] Hence, a large proportion of midlife women are susceptible to developing an insomnia syndrome that manifests predominantly with a sleep maintenance problem when they experience nocturnal hot flashes. Moreover, insomnia related to hot flashes can persist for a long period of time into the postmenopause as they last on average 7.4 years.[8] Importantly, insomnia is emerging as a possible modifiable risk factor in the development of cardiometabolic disease (CMD) including cardiovascular disease (CVD) and Type 2 diabetes mellitus. Therefore, the protracted exposure to hot flashes and sleep disturbance may have critical implications for the development of CMD in midlife women.

B. Significance of Selected Topic

Rates of incident CVD in postmenopausal women are 2- to 3-fold higher than in age-matched premenopausal women.[9,10] Moreover, surgically induced menopause also increases the risk for CVD and women who reach menopause at an earlier age (~40 years) also have higher rates of CVD than women who reach menopause later (~50 years),[10–12] indicating that the CVD risk increase is not merely an effect of chronological aging. The menopausal transition is characterized by deleterious changes in several CVD risk factors including increased fasting glucose, blood lipids, blood pressure, and body fat.[13–16] Approximately 3.8 million women ages 45–64, significantly higher than the 1.85 million women of reproductive age (18–44 years), have diabetes.[17] The prevalence of pre-diabetes in midlife women is also high,[18,19] with 34-38% meeting criteria and at risk for progression to diabetes. Postmenopausal women also adverse changes in lipid metabolism and circulating lipid levels including significantly higher levels of

total cholesterol, triglycerides, LDL cholesterol.[20,21] Importantly, these changes in lipid levels remained significant after adjusting for age, BMI and other potential confounding variables.[20]

There is a strong independent association between sleep disruption and increase in CVD risk.[22–24] A meta-analysis of 17 cohort studies showed significant increase in the rates of CVD mortality and risks of individual types of CVD, including myocardial infarction (MI), coronary heart disease (CHD), and stroke.[25] Underlying risk factors are also independently associated with insomnia. For example, the presence of insomnia significantly increases the risk of pre-diabetics to developing diabetes mellitus.[26] In a cohort of 81,233 people with pre-diabetes, 24,146 (29.7%) had insomnia at some point during the 4.3-year observation period. After adjustment for traditional risk factors, those with insomnia were 28% more likely to develop Type 2 diabetes than those without insomnia (hazard ration [HR] 1.28; 95% confidence interval [CI] 1.24–1.33). The estimate was unchanged after adjusting for baseline HbA1c level (HR 1.32; 95% CI 1.25–1.40) or fasting glucose (HR 1.28; 95% CI 1.23–1.33). These findings[26] suggest that midlife pre-diabetic women who have a high prevalence of hot flash related insomnia are at especially high risk of developing Type 2 diabetes. *Importantly, the therapeutic translation of these results point to treatment of insomnia in midlife women with hot flashes as an effective intervention for attenuating deleterious changes in CVD risk factors*.

Treatment options for menopause- and hot flash-related insomnia have received little attention to date.[27] We showed that cognitive behavioral therapy for insomnia (CBTi) is an effective treatment for insomnia in women with insomnia symptoms and hot flashes.[28] For women with hot flashes, we have demonstrated that nonbenzodiazepine GABA-A receptor modulators can treat insomnia linked with hot flashes.[29–31] Whereas hormone therapy improves sleep quality, its efficacy for sleep disturbance is less clear in women who have the more severe chronic insomnia.[27] *While evidence supports use of these agents, there is an important unmet need as their acceptability is limited by their side effects and risks, particularly breast cancer, cardiovascular, and cognitive risks emerging with long-term use*.

C. Previous Clinical Studies

Clinical data show that plasma orexin levels are 3 times higher in women following than preceding menopause, and that hormone therapy significantly reduces plasma orexin levels in postmenopausal women.[32] Preclinical studies indicate that orexin plays a role in thermoregulation.[33] Together, these findings suggest that falling levels of estradiol across the menopausal transition likely induce a concurrent increase in orexin activity, which in turn may contribute to hot flashes. *Therefore, suvorexant may play a dual role in improving sleep in midlife women with hot flash-associated insomnia by directly reducing wakefulness and concomitantly reducing hot flashes through orexin antagonism*. Consistent with this rationale, in our recently completed clinical trial of suvorexant in midlife women with insomnia and hot flashes, we found that 4 weeks of suvorexant treatment significantly improved insomnia severity and reduced nighttime hot flash frequency relative to placebo (**see Preliminary Data**). Given the prevalence of insomnia characterized by hot flashes and sleep maintenance problems in midlife women, the particular efficacy of suvorexant for middle-of-the night sleep disturbance makes it an optimal agent for this population. Its safety profile and long-term tolerability make it an ideal strategy for use in midlife women.[34]

Although we did not assess metabolic outcomes in our recent suvorexant in midlife women with insomnia, results from other preclinical studies and open-label trials of suvorexant indicate that orexin antagonism may improve glucose metabolism by improving sleep. Two to four weeks of daily administration of suvorexant in *db/db* (leptin receptor deficient) mice as a model of diabetes improves sleep duration and

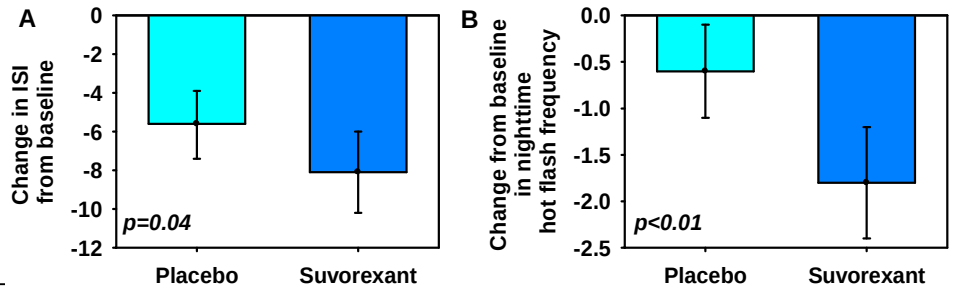
impaired glucose tolerance.[35] This improvement was associated with reduced hepatic expression of markers related to gluconeogenesis, without changes in glucagon levels. Importantly, these improvements were only evident when suvorexant was administered at the beginning of the rest (i.e., sleep) phase in these mice, and not when suvorexant was administered at the beginning of their active (i.e., wake) phase. Furthermore, orexin antagonism in streptozotocin-induced type 1-like diabetic mice neither alters sleep nor improves glucose intolerance,[36] indicating that the improvement in glucose metabolism observed with orexin antagonism is mediated by improvement in sleep. Open-label studies of suvorexant are consistent with these preclinical studies and lend further support for the use of suvorexant for insomnia as a means to improve glycemic control. Acute (3 days)[37] and chronic (4 to 8 weeks)[38] administration of suvorexant in Type 2 diabetic patients with insomnia and psychiatric patients with insomnia, respectively, improved 24-hour mean glucose levels and fasting glucose levels, respectively. Although there are few studies of suvorexant on other metabolic outcomes (e.g., lipid levels, blood pressure), multiple studies have demonstrated the association between insomnia and metabolic syndrome, including in midlife women.[37] Alterations in HPA axis and/or sympathetic nervous system activation, inflammation, and oxidative stress, which impacts glucose and lipid metabolism, blood pressure regulation and body fat deposition, are affected by insomnia and may be in the causal pathway.[37–39] *Taken together, these data potentially implicate orexin in the mechanism underlying the emergence of hot flashes and related sleep disturbance and provide a specific justification for testing the efficacy of orexin receptor antagonists in the treatment of hot flash-related insomnia as a means to improving cardiometabolic endpoints with a particular focus on glucose metabolism in midlife women.*

D. Preliminary Data

Preliminary data relevant for the current proposal derive from two studies. (1) Our *MISP-funded hot flash-related insomnia study of suvorexant* in midlife women. In a parallel-arm, double-blind, placebo-controlled trial, 60 women meeting clinical diagnostic criteria for chronic insomnia, Insomnia Severity Index (ISI) score ≥15 associated with nighttime hot flashes and >30 minutes of self-reported wake after sleep onset (WASO) were randomized to receive suvorexant 10-20 mg or matching placebo for 4 weeks. The primary outcome was the within-person change in ISI between baseline and Week 4 and the analysis adjusted for baseline score and race (which differed between groups). The manuscript reporting results of this trial are currently in review at *Sleep* (Rahman, et al). (2) Our ongoing *NIH-funded experimental study of changes in behavioral and endocrine biomarkers of weight gain induced by menopausal sleep fragmentation*. Results are presented from 22 premenopausal women who completed 5-night inpatient studies during the mid/late follicular phase of the menstrual cycle (high estradiol state). All women subsequently completed the same 5-night inpatient study after hypo-estrogenism was induced by leuprolide administration to recapitulate the estradiol withdrawal of the menopause transition. Each inpatient study was comprised of 2 nights of 8-h undisturbed time in bed (TIB) followed by 3 nights of 9-h TIB that included ~1 h of experimentally induced WASO using a 2-min acoustic stimulus repeated every 15 min throughout the sleep episode (34 total interruptions to accumulate ~68 minutes of WASO), allowing up to ~8 h of TST. Sleep was assessed by polysomnography nightly. Next-morning fasting blood samples were assayed for metabolic endpoints including glucose 4 times in each participant (during the undisturbed and fragmented sleep nights in the high and low estradiol state). We recently piloted the identical protocol in 5 healthy young men to assess the impact of sleep fragmentation on metabolic outcomes in men, and to assess sex differences in metabolic responses to sleep fragmentation.

Suvorexant treatment improves insomnia severity in midlife women with hot flash related insomnia (PMID: 35022783): In the suvorexant and placebo groups, the mean ISI score at baseline was 18.1 (95% CI 16.8–19.4) and 18.3 (95% CI 17.2–19.5), respectively (p=0.81). After adjusting for baseline ISI score and race, the within-person reduction in ISI score was significantly larger (p=0.04) in the suvorexant group (-8.1, 95% CI -10.2 to -6.0)] compared to placebo (-5.6, 95% CI -7.4 to -3.9) (**Figure 1A**). Additionally, compared to placebo, the suvorexant group had a higher proportion of responders (i.e., ≥8 point improvement on ISI, n=9/29 vs. n=11/27, respectively; relative risk 1.3 [0.7 to 1.7]; adjusted odds ratio 1.9 [0.6 to 6.2]) and a significantly higher proportion of remitters (i.e., final ISI score <8, n=2/29 vs. n=9/27, respectively; relative risk 1.4 [1.1 to 1.9]; adjusted odds ratio 8.7 [1.4 to 53.4]).

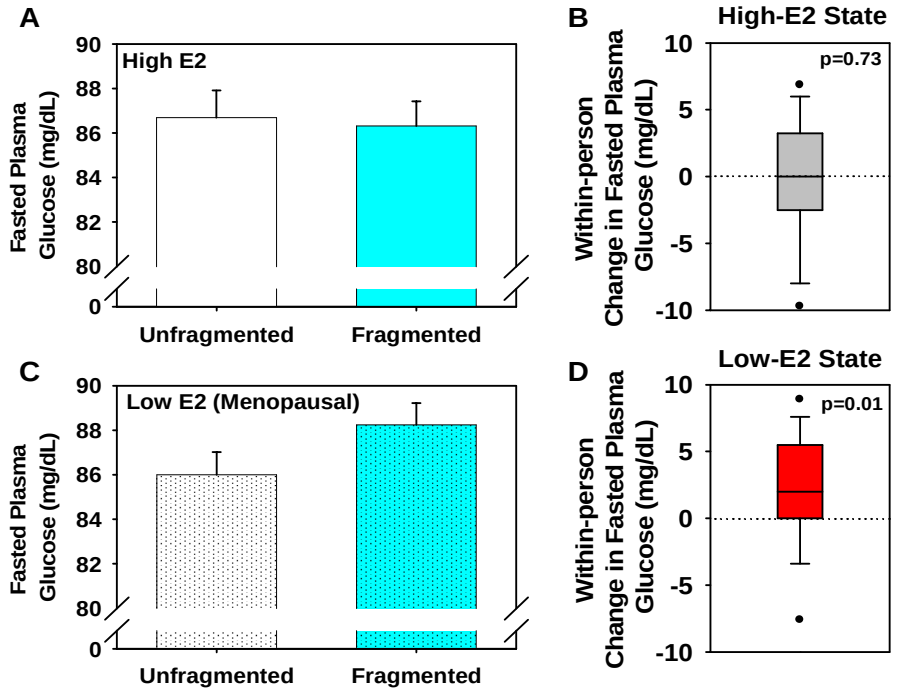
Figure 1: Change from baseline in insomnia severity as assessed using Insomnia Severity Index (ISI) (A) and average frequency of diary-reported nighttime hot flashes (B).



Suvorexant treatment improves sleep fragmentation in midlife women with hot flash related insomnia: On average, WASO decreased by ~31 min with suvorexant and by ~13 min on placebo at 4 weeks relative to baseline (p=0.05), though was not statistically significant after false discovery rate (FDR) adjustment (FDR-adj p=0.12). Within-person improvement in the number of nighttime hot flashes on the diary was 3 times greater with suvorexant as compared to placebo (FDR-adj p<0.01, **Figure 1B**). Daytime hot flash frequency tended to improve more on suvorexant than on placebo, although this was not statistically significantly different.

Sleep fragmentation increases fasting plasma glucose only in the context of a hypo-estrogenic state: Fasting plasma glucose was not changed (p=0.73) by sleep fragmentation compared to unfragmented sleep in young healthy women while they were in a high-estradiol state (**Figure 2A, B**). In contrast, when the same women were studied under low-estradiol conditions, fasting plasma glucose was significantly elevated following 3 nights of experimental sleep fragmentation (**Figure 2C, D,** p=0.01). Importantly, TST, which does not shorten across menopause or with hot flashes,[7,39] was not different between the unfragmented and fragmented conditions, both by design and verified by polysomnography. Therefore, these results indicate that women are differentially more sensitive to adverse changes in glucose metabolism in response to sleep fragmentation when they are hypo-estrogenic, consistent with the postmenopausal state. Furthermore, in our pilot study of the identical sleep fragmentation protocol in 5 healthy non-diabetic men, we found no change in fasting plasma glucose induced by sleep fragmentation as compared to unfragmented sleep, consistent with the finding in women during the high-estradiol state. These findings further motivated us to focus our studies in midlife postmenopausal women who are likely to have a unique adverse response in glucose metabolism with hot-flash related sleep fragmentation in a hypo-estrogenic state.

Figure 2: In young healthy non-diabetic women, fasting plasma glucose unchanged by experimental sleep fragmentation compared to unfragmented sleep (A, B) in a high-estradiol (E2) state consistent with premenopausal, but significantly increased by sleep fragmentation in a low-estradiol state consistent with postmenopause (C, D).



Summary of preliminary data: Taken together these preliminary data highlight that for women with hot flash-related insomnia whom we propose to study: 1) suvorexant treatment reduces insomnia severity compared to placebo, and 2) sleep fragmentation in the low-estradiol state mimicking menopausal sleep fragmentation rapidly increases fasting glucose levels. ***These findings make midlife pre-diabetic women an ideal population in whom to investigate the efficacy of suvorexant to improve both insomnia severity and glycemic control, which in the long run may reduce the risk of progression to Type 2 diabetes mellitus.***

2. Specific Aims and Objectives

STUDY AIMS: To determine the effect of suvorexant on insomnia symptoms in midlife women with using a randomized cross-over placebo-controlled trial.

PRIMARY HYPOTHESIS:

1. Relative to those assigned to placebo, participants randomized to suvorexant will show greater improvement in:
    a. Insomnia severity as assessed by insomnia severity index.
    b. Exploratory: wake-time after sleep-onset.

SECONDARY HYPOTHESES

2. Relative to those assigned to placebo, participants randomized to suvorexant will show greater improvement in:

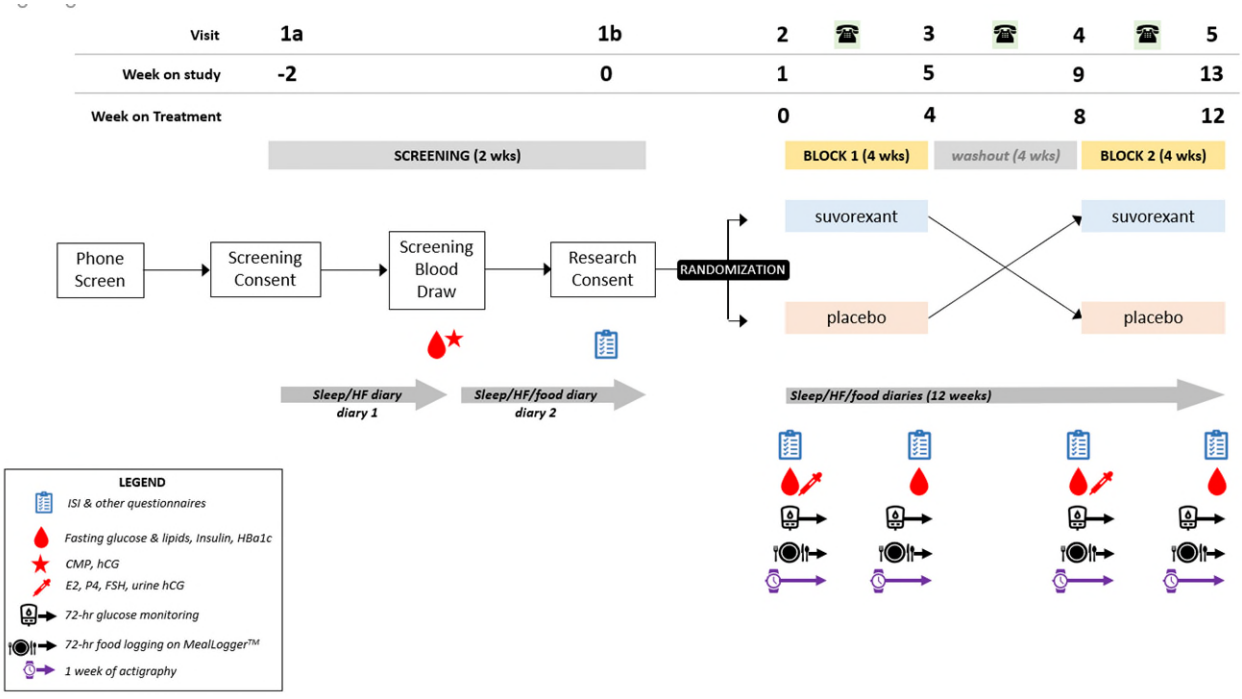
a. The proportion of participants with improvement in one or more cardiometabolic risk factors*..
b. Exploratory: mean levels of individual cardio-metabolic risk factors.

3. Improvement in levels of cardio-metabolic risk factors will be positively correlated with:
a. Greater improvement in insomnia severity.
b. Greater reduction in wake-time after sleep-onset.

3. General Description of Study Design

This is a double-blind, randomized placebo-controlled crossover trial investigating the effects of suvorexant (20 mg) on insomnia symptoms and metabolic health in midlife women with insomnia and pre-diabetes. Study procedures will involve up to 6 visits conducted over a 14-week period (2-week screening period, 4-week treatment period [Block 1], 4-week washout, 4-week treatment period [Block 2]). All study procedures will be conducted either remotely or at Brigham and Women's Hospital, Harvard Medical School, with the option for blood draws at visits 1a, 3 and 5 to be obtained at BWH outpatient CCI research sites or the participants' local Quest phlebotomy location.

The trial will investigate the impact of suvorexant treatment on insomnia symptoms (primary outcome measure) in this unique population of midlife women with cardiometabolic risk factors. The secondary endpoint will be fasting glucose. Exploratory endpoints include diary-reported WASO and 24-hour mean glucose levels.



4. Subject Selection

A. Inclusion/Exclusion Criteria for full study participants

Up to 61 women will sign Research Consent forms and be assessed for final eligibility in order to achieve our projected sample size of 34 completed participants. In order to more efficiently screen participants, up to 183 women will first sign a Screening Consent to complete initial screening procedures (1 blood draw and symptom diaries; see section 5.3 below). We anticipate ~3:1 ratio of screen fails to initially eligible participants. Eligibility will be evaluated initially through a telephone call screening process and then established by study clinicians after a medical assessment and lab results. The following inclusion and exclusion criteria will be applied:

Inclusion Criteria:

1. Healthy women aged 40–65 years
2. Postmenopausal and late perimenopausal women
3. Meets DSM-5 criteria for Insomnia Disorder
4. Score on the Insomnia Severity Index (ISI) measure ≥15
5. Subjective and sustained sleep disruption during screening
    a. 1st and 2nd week sleep diary: WASO must be 30+ minutes, and
    b. 2nd week sleep diary: WASO does not change by more than 50% of 1st week WASO
6. Experiencing hot flashes, at least some of which occur at night
7. Pre-diabetic per ADA guidelines OR have abnormal levels of one or more of the following, per AHA-defined metabolic syndrome and atherosclerotic cardiovascular disease risk factors:
    a. HDL (< 50 mg/dL)
    b. LDL (⩾ 130 mg/dL)
    c. Total cholesterol (⩾ 200 mg/dL)
    d. Triglycerides (⩾ 150 mg/dL)
    e. Blood glucose (⩾ 100 mg/dL)
    f. Current diagnosis of hypertension
    g. HbA1c from 5.70% to <6.50%

Exclusion Criteria:

1. Sleep factors:
    a. Diagnosis, or strong clinical suspicion, of other primary sleep disorders: obstructive sleep apnea, periodic limb movement disorder, narcolepsy, or cataplexy, or RLS
    b. Shift worker
    c. Use of hypnotic medications more than twice per week
    d. Unwillingness to refrain from taking any sleep medications during the study period
2. Psychiatric factors:
    a. Current major depressive episode
    b. Suicidal ideation
    c. Lifetime history of bipolar disorder, psychosis, or other serious mental health problem
    d. Current alcohol/substance use disorder
3. Medical factors:
    a. Current or prior diagnosis of diabetes mellitus
    b. Use of an insulin sensitizer or a pharmacologic treatment for pre-diabetes
    c. BMI ≥ 40 kg/m^2

   d. Renal or hepatic disease judged to interfere with drug metabolism and excretion
   e. Pregnancy or breastfeeding
   f. Malignancy within past 2 years
   g. Major surgery within past 3 months
   h. Neurological disorder or cardiovascular disease raising safety concerns about use of suvorexant and/or judged to interfere with ability to assess efficacy of the treatment
   i. Medical instability considered to interfere with study procedures
4. Concomitant medications with drug interaction or co-administration concerns
5. Contraindications or allergic responses to suvorexant
6. Lifestyle and other factors:
   a. Recent travel across 2 or more time zones
   b. Greater than 6 cups of coffee per day
   c. Greater than 15 cigarettes per day
   d. Unwilling to limit alcohol, nicotine, and caffeine consumption during study
7. Adherence factors:
   a. Ability to adhere to study procedures completed between screening and randomization visits

Off-Study Criteria:
Subjects will be dropped from the study if any of the following:

1. Meeting criteria for a current episode of major depression on the Patient Health Questionnaire 9 (PHQ-9) or depressive symptoms that are deemed by the study clinicians to be too severe to continue with study procedures
2. Emergence of suicidal ideation; homicidal ideation, or psychotic symptoms
3. Initiation of stimulants, new medications for sleep, hormonal medications, or other contraindicated medications
4. Evidence of abuse or misuse of study medications
5. Development of any significant medical problem
6. Pregnancy or breastfeeding
7. Enrollment in another clinical trial involving study procedures or medications that might put subject at risk for drug interactions or interfere with study procedures.
8. Significant deviation from study protocol or protocol violation
9. Serious side effect from study medication
10. Inability to tolerate a dose of 20-mg/day of suvorexant

Participants who are dropped from the study will be asked to complete final questionnaires remotely. In this case, vitals will not be collected, and adverse event monitoring will be completed over the phone.

B. Diversity and Inclusion
The study will focus on midlife women, the population for which 1) midlife confers unique risks, 2) the risk for comorbid chronic insomnia is especially high, and 3) for which we have the most investigative experience and preliminary data. Men and women who are outside of the midlife age range (40-65 years) will therefore be excluded. Restriction to women only and to those who are postmenopausal or in the late perimenopause is motivated by our preliminary findings that the adverse effects of sleep fragmentation on metabolic health were seen only in hypo-estrogenic women. We expect to recruit a proportion of minority participants similar to that we have recruited into previous studies of midlife women with insomnia: 15% ethnic minorities and 40% racial minorities.

We have carefully considered relevant biological variables when designing the proposed study. There are no race- or ethnicity-related exclusions to participation in the study; all individuals who meet eligibility criteria will be offered the opportunity to participate in the study without regards to racial or ethnic background. We will use recruitment strategies similar to those we have used in previous studies to enhance enrollment of racial and ethnic minorities into our studies and assess our sample repeatedly to ensure that we are enrolling a racially and ethnically diverse population. In the case that we fall short on projected total sample, or we are not enrolling a representative sample, we will conduct targeted outreach to ensure adequate numbers are achieved.

C. Recruitment Methods

Subjects will be recruited from the community around Boston by contacting previous research participants who have indicated they could be recontacted for research purposes, using Partners RALLY, and posting Sponsored Facebook/Instagram ads. All e-mail communications will follow MGB policies. We have used these methods successfully to accrue a similar population of 60 midlife women to a prior placebo-controlled clinical trial of suvorexant to treat menopause-related insomnia (#2016P002667).

Recontacting prior research participants

Participants may be recruited because they previously participated in a research study and gave written permission to be recontacted for research purposes. In that case, the investigator of the previous study, or their approved study staff, will inform potentially eligible subjects about the option to participate in the current study and, if subjects are interested, will ask them to contact the current study staff for further eligibility determination.

Facebook/Instagram advertising

We will post Sponsored Ads on Facebook/Instagram (which are the same company and use the same platform for advertising) to recruit participants to this study using the same procedures we have employed for prior IRB-approved studies (e.g. #2019P003396). Sponsored Ads are paid advertisements that we post from the Women's Hormones and Aging Research Program Facebook page. The ad text and images will be IRB-approved, and when clicked, will link directly to the IRB-approved pre-screen survey on REDCap. Due to Facebook's Personal Attributes policy, which prohibits all Sponsored Ads from including language specific to personal attributes, including gender and age, the Ads will not specifically address eligibility criteria. Instead, a summary of eligibility criteria will be listed at the top of the pre-screen survey, which participants will view prior to completion of any survey fields.

Facebook/Instagram ads will be targeted to women, ages 40 – 65, within a 50-mile radius of zip code 02115. Even though these characteristics cannot be included in the text or images for ads that are displayed to viewers, we can select these characteristics for Facebook/Instagram to filter on when determining which users to target for displaying these ads.

Since Facebook does not permit turning off comments on Sponsored Ads, we will regularly monitor the account for notification of comments. When notified a comment has been made on an ad, research staff will "hide" that comment, which makes the comment unavailable to other viewers. Research staff will not respond to questions or comments made on ads.

Recruiting through Research Patient Data Registry (RPDR)
Potential participants will be identified using RPDR by searching for MGB patients who meet selected eligibility criteria for this protocol. To contact these potential participants, we will utilize the Patient Gateway messages sent directly to active patients by sending an IRB-approved letter for recruitment.
We will send up to 2 letters, at least 1 week apart. If we do not receive a response after 2 weeks, we may follow up by phone and will call the patient up to 2 times. If we are unable to reach a patient, we will mark them as not interested in this study. Patients who have opted out of recruitment messages will be filtered out of the RPDR recruitment list and will not be sent a Research Invitation. Any patient who responds to a message requesting to be removed from the recruitment list will not be contacted again.

Recruiting through ResearchMatch
Potential subjects may be identified and recruited using ResearchMatch, a national registry for people interested in participating in research studies.

5. Subject Enrollment

Screening period: There are 5 steps to our screening and eligibility procedures:

1) a pre-screen survey on REDCap,
2) an initial pre-screening conducted over the phone,
3) a remote Screening Consent visit (V1a),
4) a screening blood draw and completion of 2-weeks of daily symptom diaries, and
5) a remote Research Consent visit (V1b)

This 2-part consent process of having a Screening Consent prior to Research Consent has been implemented successfully in other protocols (e.g. 2021P002586).

1. Pre-Screen Survey on REDCap
Recruitment methods and advertisements will refer interested participants to a REDCap prescreen survey; identifiable information only will be requested after someone passes initial eligibility questions. If interested potential participants are likely to be eligible, they will be asked for contact information and notified that a research coordinator will reach out to them to conduct the telephone screen.

2. Telephone Pre-Screening (remote)
Telephone screens will be conducted by trained research staff. Consent to screen will be obtained orally on the phone for the initial screening procedures and diaries. Individuals who provide oral consent and are interested in participating in the study will complete the ISI to assess insomnia severity, the PHQ-2 to screen for depression, and the Berlin Questionnaire to screen for sleep apnea. They will also be asked questions about their menstrual and health history, health habits, and current medications. Those who still meet eligibility criteria will be asked to complete a Screening Consent visit (V1a).

3. V1a - Screening Consent Visit (remote)
The Screening Consent visit will be conducted remotely. A member of the study team will review the study protocol and obtain written informed consent from the participant to complete the following screening procedures:

a. 1 blood draw to run screening labs needed to determine eligibility (glucose, lipids, insulin, HBa1c, CMP, and hCG). If late peri-menopausal status is unclear from menstrual history responses on the telephone screen, FSH will also be run.

Participants will be directed to a convenient BWH outpatient CCI research site or a local Quest phlebotomy location for this blood draw. The screening testing may be repeated if needed.

b. Completion of daily symptom diaries for 2 weeks

4. V1b – Research Consent Visit (remote)

If the participant meets eligibility criteria related to screening labs and daily symptom diaries, she will proceed to V1b, the Research Consent Visit. At this visit, written informed consent will be obtained from a study clinician and final eligibility criteria will be assessed, including a clinical interview to diagnose an insomnia disorder and to ensure that participants with contraindicated sleep, metabolic, psychiatric, and other medical problems and medications are excluded. The screening testing may be repeated if needed. Risks and benefits associated with use of suvorexant will be described.

No medication will be provided. In advance of the Randomization Visit (V2), all eligibility assessments will be reviewed for definitive eligibility.

6. STUDY PROCEDURES

At all visits, adverse events will be assessed, and concomitant medications will be reviewed. Actigraphic watches and glucose monitors will be distributed and collected at in-person visits and by mail (paid for by the study) as applicable.

Randomization Plan

Suvorexant and identical placebo will be obtained from Merck and stored in the Brigham and Women's Hospital Investigational Drug Service. The Research Pharmacist will generate a confidential randomization schema using a block size of 4 to determine that approximately 50% of participants will take suvorexant in the 1st treatment block and placebo in the 2nd treatment block, and approximately 50% of participants will take placebo in the 1st treatment block and suvorexant in the 2nd treatment block. Study participants and all study personnel, including those entering data, will be blinded to the assignment. Only the Research Pharmacist will be unblinded to treatment assignment.

Treatment period (4 study visits)

Participants will have a study visit at the start and end of each 4-week treatment block. Study procedures conducted during and surrounding these visits are the same (minor differences noted below):

- Blood draw for research assays (glucose, insulin, lipid profiles and HbA1c; stored serum if consent given)
- Questionnaires (ISI, PSQI, PHQ-9, CESD, GAD7, MENQOL, CGI)
- Wear glucose monitor for 72 hours
- Complete 1 week of actigraphy
- Complete 1 week of symptom diaries
- Complete 3 days of food logging on MealLogger

Specific to V2 and V4 (start of each treatment block):
Vital signs will be taken at the start of V2 to confirm final eligibility prior to medication dispensing.

- Vital signs and body measurements
- Blood draw will include reproductive hormone assays
- Urine will be collected for urine hCG

- Participants will be provided a one-month supply of blinded study drug with instructions for use

Specific to V3 and V5 (end of each treatment block):

- Will preferably be conducted in-person at BWH, including the blood draw, vital signs, and body measurements.
- Alternatively, these visits may be conducted remotely via video call if preferred by participants in order to assure participant retention. The only study procedure required to be in-person is the blood draw. Participants completing V3 and V5 remotely will be directed to a convenient BWH outpatient CCI research site or a local Quest phlebotomy location for this procedure. These women will not be able to provide the additional blood sample for future assays nor obtain vital signs and body measurements.

3 telephone check-ins will be conducted by study staff midway through each Block. Spontaneously reported adverse events will be recorded.

TABLE OF PROCEDURES

		SCREENING				INTERVENTION				
						BLOCK 1		WASHOUT	BLOCK 2	
	Visit Type	Pre-V1	V1a Screening Consent	Screening blood draw	V1b Research Consent	V2 Random-ization	V3		V4	V5
	weeks on medication		-2		-1	0	4		8	12
General/ Screening Procedures	Screening Consent		X							
	Demographics		X		X					
	Research Consent				X					
	Medical & Personal History Questionnaire				X					
	Concomitant Medications				X	X	X		X	X
	Diabetes Assessment				X					
	Insomnia DSM-V Diagnostic Assessment				X					
	Berlin	X								
	Screening Assays			X						
	Reproductive Hormone Assays					X			X	
	Urine Pregnancy Test					X			X	
Vitals & Morphometrics	Height/Weight/Heart rate/Blood pressure/Body Measurements					X	X		X	X
Adverse Event Reporting					→	→	→	→	→	→
Medication	Dispensing & Instructions					X			X	
	On Medication					→	→	→	→	→
Sleep Assessment	ISI	X			X	X	X		X	X
	Actigraphy Watch[a]				→	→	→	→	→	→
	Sleep & Hot Flash Diary[a]		→	→	→	→	→	→	→	→
	PSQI					X	X		X	X
Metabolic Assessment	glucose monitoring[b]				→	→	→	→	→	→
	Food Diary[a]			→	→	→	→	→	→	→
	MealLogger™ [b]				→	→	→	→	→	→
	Research Assays					X	X		X	X
Mood and Quality-of-Life Measures	PHQ-2	X								
	PHQ-9				X	X	X		X	X
	CES-D					X	X		X	X
	GAD-7					X	X		X	X
	MENQOL					X	X		X	X

Study procedures completed between study visits: a = for 1 week; b = for 3 days

DSM-V=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, GAD-7=Generalized Anxiety Disorder Scale, ISI=Insomnia Severity Index, MENQOL=Menopause-Specific Quality of Life Questionnaire, PHQ-2=Patient Health Questionnaire Depression Screen, PHQ-9=Patient Health Questionnaire Depression Scale, PSQI=Pittsburgh Sleep Quality Index

Procedures and Measurements

1. *Insomnia and sleep quality symptoms* will be measured using:
    1. *DSM 5 diagnostic interview for chronic insomnia.* A clinical diagnosis of chronic insomnia will be made using the DSM-V diagnostic interview, allowing for associated hot flashes
    2. *Sleep diary*. Consistent with research consensus guidelines of insomnia,[40] a standard daily sleep diary will be completed to quantify perceived total sleep time, sleep latency, wake time after sleep onset, number of awakenings, sleep efficiency, and sleep quality.
    3. The *Actiwatch actigraphic watch* (Condor Instruments, São Paulo, Brazil) will be worn on the non-dominant wrist to quantify sleep patterns based on acceleration and movement and the data output will be analyzed using standard actigraphic analysis algorithms.
    4. The *Insomnia Severity Index (ISI)*, a 7-item self-rated questionnaire (range 0–28) used to assess the severity of insomnia symptoms over the past 2 weeks.[41]

5. The *Pittsburgh Sleep Quality Index (PSQI)*, a 19-item self-rated measure of global sleep quality (range 0–21) occurring during the past one-month.[42]

2. *Sleep apnea* will be screened out using a combination of self-reported prior diagnosis and the Berlin Questionnaire, an 11-item questionnaire, to exclude women likely to have obstructive sleep apnea.
3. *Metabolic measures* will include:
    1. *Fasting plasma glucose, insulin, lipid profiles, HbA1c.* Assessed by CLIA-certified commercial laboratory blinded to study conditions.
    2. *Meal diary.* A daily meal diary with be provided with instructions on how to record content and quantity of food consumed each day.
    3. *Glucose monitoring*. Assessed using a clinical grade ambulatory continuous glucose monitor (Abbott FreeStyle Libre 14 day system) consisting of the reader and a glucose sensor worn on the back of the upper arm. Use of these glucose monitors has been approved in other BWH research studies (e.g., 2015P002470).
    4. *MealLogger,* allows participants to take a time-stamped photograph of their meal, include a detailed description of the meal content and where it was prepared (e.g., home vs. restaurant), identify which meal they are eating (e.g., breakfast, lunch, dinner, or snack), and whether they are eating alone or with at least one other person. BWH dieticians will assess the meals for caloric and nutrient content using the University of Minnesota Nutrition Data System for Research software. Our research team has previously utilized this software application (protocol 2016P002821). MealLogger is easily installed on both Android and iPhone systems and is used both in research studies and in the general population.
4. *Mood and quality-of-life measures*:
    a. *Patient Health Questionnaire 2-item (PHQ-2),* a 2-item self-rated questionnaire to screen for depression based on DSM criteria that inquires about the frequency of depressed mood and anhedonia over the past 2 weeks.[43]
    b. *Patient Health Questionnaire 9-item (PHQ-9)*, an 9-item self-rated measure of depression based on DSM criteria that assesses core psychological and neuro-vegetative symptoms of depression occurring over the past 2 weeks.[44]
    c. *Center for Epidemiological Studies Depression Scale (CES-D)*, a 20-item self-rated scale (range 0–60) that measures the severity of predominantly psychological symptoms of depression experienced over the past week.[45]
    d. *Generalized Anxiety Disorder Assessment (GAD-7)*,[46] is a 7-item instrument that is used to assess the severity of anxiety symptoms over the past two weeks.
    e. *Menopause-Specific Quality-of-Life Questionnaire (MENQOL)*,[47] a widely used 33-item self-rated questionnaire about quality-of-life specifically in menopausal women.
5. *Additional assays*:
    a. *Reproductive hormones* (FSH, estradiol, progesterone) will be measured in serum to characterize the hormonal profile of the study population.
    b. *Pregnancy test* will be obtained using serum and urinary HCG testing to screen out pregnancy.

Study Drug To Be Used

Up to 45 eligible women will be randomized to receive either a) suvorexant in the 1st treatment block and placebo in the 2nd treatment block, or b) placebo in the 1st treatment block and suvorexant in the 2nd treatment block. Participants will be given a one-month supply of blinded study medication (suvorexant 20-mg or placebo) at the start of each treatment block and instructed to take the medication at bedtime each night for 4 weeks. After the 1st treatment block, participants will have a 4-week washout period when they will not take any study medication. At the start of the 2nd treatment block, participants will be given

a one-month supply of study medication, and again instructed to take study medication at bedtime each night for 4 weeks. Blinded medication will be provided by Merck as the study sponsor.

Remuneration
To recognize participants for the time and effort involved in completing all study procedures, subjects will be compensated up to $800, prorated based on their progress through the study. Participants will be paid $100 for screening ($25 for V1a and $75 for V1b), $100 after completing V2 procedures, $200 after completing V3 procedures, $100 after completing V4 procedures, and $300 after completing V5 and all study procedures. Parking vouchers will be provided, and, if needed, transportation to and from study visits will be reimbursed (up to $25/one-way).

Stored Blood Samples
At the Research Consent Visit, participants will have the option to consent to have additional blood drawn at each study visit, which would be stored and used for future analyses related to the focus of this study. Prior to conducting future assays on these stored blood samples, the protocol will be amended to include additional assays and analysis plans.

7. Risks and Discomforts

All study procedures will be approved by the Mass General Brigham IRB before being initiated. Participants will be informed that they are free to withdraw from the study at any time and that withdrawing will not have any adverse effects on their medical care within Mass General Brigham. Potential risk to study subjects is minimized by the frequent assessments required by the study design. Careful screening procedures, including medical history and evaluation, laboratory tests, and psychological interviews, will facilitate the identification of any medical problems and potential adverse events so that subjects can be treated appropriately.

Adverse Events:
Adverse events requiring medical attention are expected to be rare in this proposal. The investigators have substantial experience conducting the proposed study procedures and managing adverse events that may result from the implementation of these procedures. In case of a serious adverse event, study medication will be unblinded and discontinued, and appropriate diagnostic and therapeutic measures will be taken, as determined by the investigator. Emergency facilities for managing any serious adverse event that requires urgent evaluation and treatment are available to the investigators. (See Section 9, “Adverse Event Reporting” for AE Reporting procedures).
Potential risks of study procedures:

1. Suvorexant*:*
Known toxicities of suvorexant include daytime somnolence, nighttime “sleep driving”, worsening of depression or suicidal thinking, compromised respiratory function, sleep paralysis, hypnagogic/ hypnopompic hallucinations, and cataplexy-like symptoms.

The most common side effects that were reported in previous studies with suvorexant included:

- Headache (7 out of 100 people reported this side effect)
- Next-day drowsiness (7 out of 100 people reported this side effect)
- Dizziness (3 out of 100 people reported this side effect)
- Abnormal dreams (2 out of 100 people reported this side effect)

- Cough (2 out of 100 people reported this side effect)
- Diarrhea (2 out of 100 people reported this side effect)
- Dry mouth (2 out of 100 people reported this side effect)
- Upper respiratory tract infection (2 out of 100 people reported this side effect)

Suvorexant may cause serious side effects that participants may not know are happening. These side effects include:

- Sleepiness during the day
- Not thinking clearly
- Acting strangely, confused or upset
- "Sleep-walking" or doing other activities when you are asleep like eating, talking, having sex, or driving a car.
- Worsening of depression or suicidal thinking

Suvorexant can cause next-day mental impairment in a dose-dependent pattern. The safety profile of the 20-mg dose used in this study has been well-established. Upon initiating treatment, subjects will be cautioned about driving and other activities requiring full mental alertness in the morning. Before taking the study drug, subjects will be advised to read the FDA-approved Medication Guide.

Steps to decrease risk:

- While unlikely in this population, a urine HCG test will be performed on all subjects at the beginning of each treatment block prior to receiving study drug to confirm that subjects are not pregnant.
- The participants will be informed that the study medication suvorexant must only be taken by the subject alone, the person for whom it was intended. In addition, the study medication must be kept out of the reach of children or persons with limited ability to read and understand.
- Adverse events will be monitored at each study visit and participants encouraged to contact the study team in between appointments if they have any concerns.
- Participants with conditions which are contraindications to suvorexant use will be excluded.

2. Blood Sampling: The risks associated with phlebotomy are minimal and include hematoma, pain, infection, and fainting spells. The maximum amount of blood drawn for this study over 13 weeks, including the optional blood draws for stored samples, is 160 mL.

Steps to decrease risk:

- All blood draws will be performed by trained personnel who use standard sterile techniques. These procedures will be included in the patient informed consent document.
- The amount of blood drawn is not enough to cause harm to subjects.

3. Psychological risks: Some women may indicate or develop a depressive episode on questionnaires, answering questions on the research instruments used to evaluate psychological symptoms can be upsetting to some women.

Steps to decrease risks:

- Any woman who self-reports on the phone screen or in the screening questionnaires and are judged by a study clinician to meet criteria for a current depressive episode will be encouraged to follow up with their primary care physician and provided referrals to mental health services. They will not be eligible for enrollment. Treatment decisions (including type of and when to initiate) will not be influenced by study participation.
- Any woman who develops depression or suicidal ideation during the study will be evaluated, withdrawn from the trial, and referred for treatment, including emergency evaluation if appropriate.
- Subjects will be told that they can skip questions that make them feel uncomfortable.
- The informed consent process will include an explicit discussion that the study is not guaranteed to provide treatment for symptoms.

4. Continuous glucose monitor*:* The sensor is small (about the size of 2 stacked US quarters) generally comfortable to wear. A very thin filament sits just under the skin to measure interstitial fluid. Some participants may find the monitor uncomfortable at first or a slight prick when the sensor is first inserted. In some participants with sensitive skin, irritation is possible.

Steps to decrease risk:

- If the participant reports discomfort or skin irritation at the site the sensor is applied then the sensor will be moved to a nearby different part of the upper arm.

5. Actigraphy: There is a risk of skin irritation while wearing the actigraphy watch. Subjects will find the device similar to wearing a regular wristwatch.

Steps to decrease risk:

- The watch can be removed during the daytime to reduce irritation if it emerges.

6. MealLogger™: MealLogger does not collect identifiable information through the software application, and participants will be instructed that the only required information is their meals. The research team will create credentials for patients using this app, so that MealLogger will not be able to associate the data with a real person. MealLogger has been approved in other BWH research studies (e.g., 2016P002821).

7. Loss of confidentiality: Should there be a breach of confidentiality regarding diagnosis, substance use, or other sensitive information, the patient might be exposed to discrimination.

Steps to decrease risks:

- All research records will be kept with maximum possible confidentiality. Results will be de-identified and subject binders will be maintained in a locked closet. No names will be used in the presentation of any data. Source documents will be reviewed only by study personnel. All HIPAA regulations will be followed.

8. Benefits

A potential benefit of participating in this study is improvement of insomnia symptoms and overall quality of life. Participants may benefit from the close monitoring of their sleep patterns, metabolic, hot flashes, and psychological symptoms. If a significant abnormality is detected on any of the study measures, that are collected participants will be informed and encouraged to follow up with their health care providers.

Information from this study may benefit others because the medical community will gain more knowledge on the efficacy of suvorexant for insomnia and metabolic health in midlife women.

9. Statistical Analysis

Data integrity, safety monitoring, and statistical analysis implementation plan: All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the BWH Research Pharmacist who generates the randomization code will be unblinded to treatment assignment.

Confidentiality will be maintained by storing data with a subject identification number only. No identifying information will be entered in the electronic database. Only the PIs, co-investigators, and study staff will have access to the database and the study binders. Data will be entered into a secure, HIPAA-compliant Research Electronic Data Capture (REDCap) database hosted by MassGeneralBrigham and analyzed using SAS (Cary, NC) and/or STATA (College Station, TX). The final database will not be unblinded until all study data are complete and entered and the Independent Safety Monitor has completed a medical and scientific review, consistent with procedures we use in our previous clinical trials.

Overview of analytic plan and study endpoints

The primary hypothesis for this trial is that suvorexant is superior to placebo in treating insomnia symptoms. The primary endpoint is the ISI score at week 4 of each Treatment Block. Additional analyses will: (1) examine the effect of suvorexant compared to placebo on: (i) the secondary endpoint of proportion of participants with improvement in one or more cardiometabolic risk factors [HDL,LDL, total cholesterol, triglycerides, blood glucose, hypertension] , and (ii)mean levels of individual cardiometabolic risk factors; (2) explore the correlation between the change (Week 1 to Week 4) in cardiometabolic risk factors with the change in ISI and WASO. All endpoint measures are continuous variables. For data collected daily during the trial (i.e., sleep diary, actigraphy, meal diary), averages across the week of data collection at the pre- and post-Block intervals will be used as point estimates.

Primary analysis

The primary analysis will test the effect of suvorexant compared to placebo using a mixed-effects model with terms for baseline value, treatment, sequence, period, and time (as a categorical variable), consistent with the analysis approach of previous randomized crossover trial of suvorexant.[47] Secondary multivariate regression analyses will be conducted using age, BMI, and hot flash frequency as pre-specified covariates.

Diagnostic methods will be used for all models to assess their distributional assumptions, model adequacy, potential outlying or influential data points, and possible carryover effects. This analytical method will similarly be used to assess secondary and exploratory outcomes. An additional exploratory ISI responder analysis will be conducted using random effects logistic regression to determine whether there is a group difference in the proportion of participants that had at least an 8-point reduction in the ISI score from baseline.[3826] Proportion of participants with improvement in one or more cardiometabolic risk factors will be compared between suvorexant and placebo using Fisher's exact. Associations of the change in cardiometabolic endpoints with changes in ISI and WASO will be assessed using generalized linear mixed models accounting for the correlated nature of the change data within individuals from each Treatment Block and the strength of the association will be estimated using simple Pearson or Spearman correlations. Correlational analyses will be conducted for the entire study population followed by stratified analyses for each treatment condition separately.

Power and sample size

To initiate treatment in 43 women, we will enroll up to 61 midlife women. This estimate is based on the screen-failure rate from our prior suvorexant trial in midlife women and the proportion of women we expect will fail our pre-diabetes screening based on the estimated prevalence of pre-diabetes in this age-group.

The planned sample size of 34 completed participants provides at least 80% power for detecting an effect size of 0.50 or larger in a two-tailed, matched-samples contrast of group-level means, consistent with our primary analysis plan to assess the difference between suvorexant and placebo on the primary endpoint of ISI scores with repeated measures. We based our estimates on our recently completed MISP-sponsored suvorexant trial in which we found an effect size of 0.5 in the reduction of ISI scores from baseline to the end of the 4-week treatment interval between suvorexant and placebo treatment arms.

For one of the secondary endpoint of fasting plasma glucose, an open-label study of suvorexant reported a reduction in fasting glucose compared to baseline with 4 weeks of treatment in a non-prediabetic population with an effect size of 0.5.[38]

9. Monitoring and Quality Assurance

Independent Monitoring of Source Data

Confidentiality will be maintained by storing data with a subject identification number only. Only the PI, co-investigators, and study staff will have access to the database and the study binders. Data will be entered into a secure, HIPAA-compliant Research Electronic Data Capture (REDCap) database hosted by Mass General Brigham. All exported data will be de-identified using only the subject's identification number. Analysis of all study data will be conducted by Drs. Rahman, Joffe, and other co-Investigators on the study in consultation with Sybil Crawford, PhD, the statistical consultant on this project. All study personnel and participants will remain blinded to treatment assignment, including staff entering study data. Only the BWH Research Pharmacist who generates the randomization code will be unblinded to treatment assignment.

Medical Monitoring Plan

A study clinician on this protocol will be appointed the Medical Monitor by the Principal Investigator. The Medical Monitor will be responsible for:

- Reviewing all safety and adverse data from all study visits weekly. Serious adverse events will be reviewed and reported to the IRB within 7 calendar days, per MGB HRC guidance.
- Meeting with the Research Coordinator weekly to review status of all active participants
- If a safety concern is identified, conferring with consenting MD, PI, and/or Independent Safety Monitor to create an action plan.

A Medical Monitoring Checklist will be developed in REDCap, which prompts the Medical Monitor to double-check lab results, vital signs, concomitant medications, adverse events, and the scores on the Patient Health Questionnaire-9 (PHQ-9) at all visits to monitor signs of depression and/or suicidal ideation.

Measures for Assessing and Responding to Depression and Suicidal Ideation

PHQ-2: The PHQ-2 will be administered during the telephone screen. The telephone script includes a line indicating that potential participants will be asked about their mental health, including depression symptoms, which will be read prior to obtaining verbal consent.

- If a potential participant's score is > 3, they will not be eligible to participate in the study. Anyone identified as being at risk for depression will be offered options to seek mental health services, such as contacting their PCP, calling BWH Psychiatry Dept, or going to an Emergency Room. If a potential participant spontaneously indicates suicidality during the telephone screen, the screener will ask them to stay on the phone while a clinician is contacted. The screener will have a list of all the study clinicians' contact and pager information in order to identify an available clinician.

PHQ-9: The PHQ-9 will be administered at Visits 1-5. Participants will be withdrawn from the study if they meet criteria for high likelihood for Major Depressive Episode using an establish diagnostic algorithm (see below) to assess likelihood of MDE from the PHQ-9. This approach provides more specificity for depression in a population with insomnia and menopausal symptoms which can inflate the PHQ-9 total score. A participant answering "1", "2", or "3" on Q9 would also be withdrawn from the study. In either of these cases, a study clinician would be available to assess the participant for need for urgent care and to refer them to mental health services, if applicable.

Diagnostic algorithm for PHQ-9:

Criterion 1: Q1 or Q2 must be "2" or "3".
Criterion 2: Considering Q1-9, at least 5 responses must be "2" or "3".
If both criteria are met, indicates high likelihood of a Major Depressive Episode.

Independent Safety Monitor

A clinician who is unaffiliated with this protocol will be appointed by the Principal Investigator to serve as the Independent Safety Monitor (ISM) for this trial. The ISM will be blinded to treatment assignment. The plan for Independent Safety Monitoring is as follows:

- In the case of a Serious Adverse Event (SAE), the study team will notify the ISM within 24 hours of becoming aware of the SAE. The ISM will review the case and, if appropriate, will examine the participant. The ISM will produce a short report on the SAE.
- The ISM will review all non-serious Adverse Events each quarter. This review and any recommended actions will be documented in the Regulatory Binder.
- Upon completion of data collection, the final database will not be unblinded until the ISM has completed all reviews, protocol violators have been identified, and all study data are complete.

Adverse Event Reporting

Subjects will be monitored closely for adverse events at every visit. Spontaneously reported adverse events relayed to the study team at each visit and between visits will be noted by research staff and reviewed by the Medical Monitor. Research staff will record adverse events using standard spontaneous IRB-approved reporting procedures. Participants will be told during the consent process that they should report any concerns about sedation and changes in mood or thoughts of self-harm immediately to the study team, using the contact information provided on the form. Participants will be informed that they can contact the investigator between visits if they have concerns about potential side effects. Routine adverse events and serious adverse events will be reported consistent with local IRB requirements and per Merck guidelines for reporting to the sponsor. In addition, the Medical Monitor and Independent

Safety Monitor will review all adverse events and investigate those considered serious and unexpected consistent with standard ISM procedures.

10. Privacy and Confidentiality

- ☒ Study procedures will be conducted in a private setting
- ☒ Only data and/or specimens necessary for the conduct of the study will be collected
- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- ☐ Additional privacy and/or confidentiality protections

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