**STUDY PROTOCOL**

# The efficacy of masked tapering on discontinuation of hypnotics in older Veterans (SWITCH study)

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## SPECIFIC AIMS

Hypnotics such as benzodiazepines and benzodiazepine receptor agonists (BzRAs or Z-drugs) are often prescribed for insomnia.[3] Among Veterans attending outpatient clinic appointments, approximately one-quarter use hypnotics (or bedtime alcohol).[4] Hypnotics use is associated with an increased risk of falls[5;6] and worse cognition[7] in older adults. Discontinuing hypnotics often attenuates or reverses these negative effects,[8;9] and the Department of Veterans Affairs (VA) has initiatives to reduce hypnotic use among older Veterans. Current discontinuation strategies focus on tapering off the hypnotic and/or treating insomnia symptoms. Common strategies include supervised gradual taper (SGT), cognitive behavioral therapy targeting hypnotic withdrawal (CBT-HW), cognitive behavioral therapy for insomnia (CBTI), and combination therapy (SGT+CBTI). Yet up to 40% of patients eventually resume use of hypnotics with these strategies, suggesting that other mechanisms need to be targeted to achieve and sustain high rates of non-use.[10;11]

Another mechanism that may be a viable target for achieving hypnotic discontinuation and sustaining long-term non-use is the placebo effect,[12-14] which is characterized by real improvements in sleep arising from psychosocial aspects of treatment rather than drug effects alone. We recently developed and tested the feasibility of an intervention that targets the placebo effect. Our intervention retains core components tested in prior studies for achieving hypnotic discontinuation (i.e., SGT+CBTI), but adds a novel feature—"masked" tapering. Masking is achieved by encapsulating hypnotics (prepared by a compounding pharmacy) so the patient, who has consented to a gradual taper, is unaware of the actual dose in each capsule until the end of the taper, when the tapering schedule is revealed to the patient. Towards the end of the taper, placebo capsules are used. Through novel cognitive exercises, the therapist uses masking as a tool to challenge expectancies about hypnotics, which may be contributing to chronic use, and to augment CBT-HW (e.g., preparing for withdrawal). Coupled with CBTI (i.e., stimulus control, sleep restriction, cognitive therapy for insomnia, and relaxation), the intervention targets the placebo effect and the factors contributing to insomnia symptoms and helps patients safely taper off their hypnotic and develop relapse prevention skills.

The objective of the proposed study is to test whether hypnotic discontinuation rates can be increased with a novel set of cognitive exercises that use supervised masked tapering as a core tool to challenge expectancies about hypnotics. In a 4-year randomized trial (N=132 participants), we will measure the effects of a 2-month program entitled, **M**asked **T**aper plus **c**ognitive behavioral therapy-**a**ugmented **p**rogram (MTcap), which combines novel cognitive behavioral therapy exercises, supervised masked hypnotic tapering, CBT-HW, and CBTI. We will compare outcomes in MTcap to a supervised unmasked (traditional) SGT+CBTI program post-treatment and at 6 months follow-up to determine whether the addition of the novel cognitive exercises and masked tapering reduces expectancies for hypnotics, improves hypnotic discontinuation rates, and improves insomnia symptoms. The rationale is that hypnotic-related placebo effects can be specifically targeted with our novel intervention. The following are the **primary aims** for the proposed project:

Aim 1: Determine whether MTcap improves hypnotic discontinuation more than SGT+CBTI post-treatment and at 6 months follow-up.

- H1a: Participants who receive MTcap will have increased likelihood of hypnotic discontinuation post-treatment and at 6 months follow-up compared with those who receive SGT+CBTI.
- H1b: Participants who receive MTcap will use less hypnotic medication post-treatment and at 6 months follow-up compared with those who receive SGT+CBTI.

Aim 2: Determine whether MTcap improves insomnia severity more than SGT+CBTI at 6 months follow-up.

- H2: Participants who receive MTcap will have lower Insomnia Severity Index scores at 6 months follow-up compared to SGT+CBTI.

Aim 3: Determine whether MTcap improves expectancies about hypnotics more than SGT+CBTI post-treatment and at 6 months follow-up.

- H3: Dysfunctional Beliefs and Attitudes About Sleep (DBAS) – Medication Scale ratings will improve compared to SGT+CBTI post-treatment and at 6 months follow-up.

A secondary aim is to compare balance and cognition in the MTcap arm compared with the SGT+CBTI arm at follow-up. We hypothesize that participants who receive MTcap will have better balance and cognition compared to those who receive SGT+CBTI post-treatment and at 6 months follow-up.

This proposed study will test the effects of an innovative intervention on chronic hypnotic use among older Veterans, which is a prevalent, high-priority, and challenging problem. The intervention was designed based on extensive feasibility testing. If successful, this novel intervention could lead be disseminated throughout the VA and lead to significant improvement in ongoing efforts to decrease chronic hypnotic use among older Veterans.

## RESEARCH DESIGN AND METHODS

Basic Study Design (Figure 1): The proposed study is a 4-year randomized trial to test the efficacy of a novel treatment program for achieving hypnotic discontinuation among older Veterans receiving outpatient prescriptions for hypnotics.

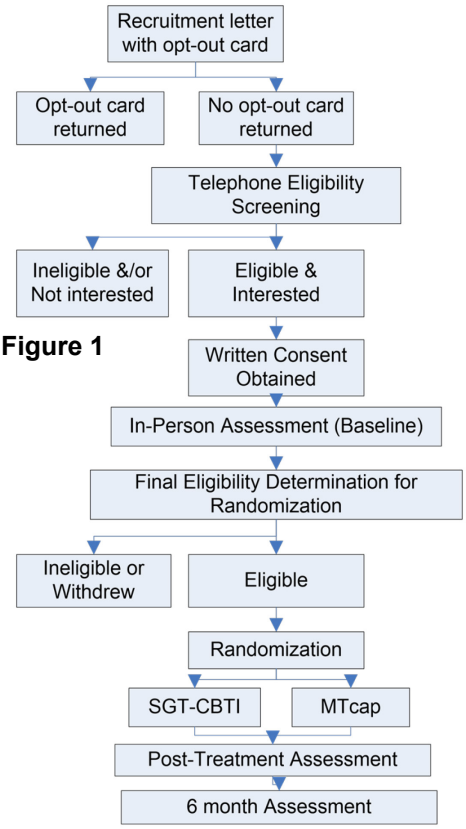



**Figure 1**

Setting: The proposed study will be performed within the VAGLA, where approximately 1,650 older Veterans receive each quarter the benzodiazepines and Z-drugs targeted in this study. All in-person study assessments and treatment sessions will be completed within VAGLA.

Specific VAGLA facilities include: West Los Angeles Medical Center, Sepulveda Ambulatory Care Center, Los Angeles Ambulatory Care Center and VA Community-based Outpatient Clinics in Lancaster, Oxnard, and Bakersfield. Our research staff may meet participants to drop/off or pick up study materials, and if necessary, to conduct baseline and follow-up assessments. Recruitment sample:

The sampling frame for this study will consist of Veterans ≥ 55 who received hypnotic prescriptions for three or more months from VAGLA pharmacies within the past year. To obtain this sample we will access VA administrative data sources, seek patient referrals from VAGLA healthcare providers, and distribute recruitment flyers in VA GLAHS outpatient clinics. Each of these recruitment strategies is described below:

1. VA Corporate Data Warehouse (CDW)

Authorized VA project team member(s) will work with VINCI programmers to pull a sample using the VA Corporate Data Warehouse (CDW). Study inclusionary criteria will be applied to select eligible Veterans for recruitment. To help capture eligible patients with fresh contact information, this process will be repeated at least 2-3 time during the study recruitment period.

The variables in the sample file will include the following:

- Unique patient identifiers (e.g. Scrambled SSN, Patient ICN, PatientSID, etc.)
- Contact information (e.g. Name, residential address, zip code, telephone numbers)
- Demographic and Veteran Characteristics information (e.g. date of birth, gender, race/ethnicity, date of death, Veteran status)
- Hypnotic medications (e.g. outpatient medication names, dose, prescription number, issue date, etc.)

A link file will be created using the sample file to associate the project specific study ID with the Veterans' unique identifier (PatientICN/PatientSID, or SSN/scrambled SSN) which can be used to access VA VINCI/CDW data. The new records pulled with each additional sample pull will be added to our link file to create a single cumulative file of all sampled Veterans. All records will be assigned a study ID number that will serve as the primary key for matching data from the additional sources. The Link File will be stored on a restricted-access folder on the CSHIIP-managed secure server behind the VA firewall and is never transferred during the project, nor will it be accessible to anyone other than authorized VA project team member(s).

We will use the same process to identify from CDW Veterans who receive care at the Tibor Rubin VA Medical Center in Long Beach (VALB). Many VALB patients live close to the VAGLA campus in West Los Angeles and may be willing to participate in the study. If these VALB Veterans enroll in the study, all study activities will be conducted at VAGLA. No study activities will be done at VALB.

We will also use the same process to identify from CDW Veterans who receive care at the VA Loma Linda Healthcare System. If these Loma Linda Veterans enroll in the study, study activities will be conducted via telehealth at VAGLA.

2. VA Academic Detailing Service Benzodiazepine/ZDrugs Dashboard

The VA Academic Detailing Service has compiled and maintains a database of VA GLAHS patients who are prescribed benzodiapezines and benzodiapezine receptor agonists (Z-drugs). This database, or dashboard, can be found on their Data Resources website. In this dashboard, the names and mailing addresses of VA GLAHS patients prescribed benzodiazepines and Z-drugs are listed along with prescribing information. We will access this dashboard to confirm the CDW sample.

The variables that will be abstracted from the dashboard will include:

- Unique patient identifiers (PatientSID, last 4 SSN)
- Contact information (name, residential address, zip code)
- Patient characteristics (age)
- Hypnotic medications (medication names, number of prescriptions, prescriber, dispensing location, prescribed for insomnia or PTSD, next primary care and mental health appointment dates and locations)

3. Consults to VAGLA Insomnia clinics

Research staff will access the VA electronic consults made to Insomnia clinic. Patients who are referred to the clinic for cognitive behavioral therapy for insomnia treatment will be identified. Study staff will then review demographic information, medications and clinic notes to determine basic eligibility criteria (e.g., age $\geq$ 55, prescribed a hypnotic medication) of these Veterans. Names, addresses and telephone numbers of Veterans who meet these basic eligibility criteria will be abstracted from the medical record by research staff and entered into a study database.

4. Referrals from VA GLAHS healthcare providers

A recruitment flyer with a cover memo to VA GLAHS providers with be distributed to providers in primary care, mental health, and sleep medicine clinics (see attached Provider Memo and Recruitment Flyer). The memo describes the study and basic eligibility criteria and invites providers to distribute the flyer to patients who might be appropriate for the study. Providers are also invited to send an encrypted email to the study team with the name and last four social security numbers of patients who may be eligible for the study. When the research team receives the name of a patient from a provider, research staff will review the CPRS electronic medical record to determine if the patient meets the basic study eligibility criteria (e.g., age, prescribed one of the targeted hypnotics to treat insomnia) (see CPRS data abstraction form). Patients who meet these criteria will receive a recruitment telephone call from research staff as described below (see telephone eligibility screening).

5. Self-referral from Veterans

We will also post the recruitment flyer (which may also be enlarged to the size of a poster board) in outpatient clinic waiting areas (our research team will seek approval from appropriate VA GLAHS authorities prior to displaying any flyers/posters) and at community sites frequented by Veterans (e.g., Veteran Centers, DAV halls, Elk Lodges, senior centers). Written permission to post the recruitment flyer at community sites, and for study staff to provide verbal information about the study, will be obtained from each site (see attached Off-site Permission form) before flyers are posted.

6. e-Recruitment: We will put information about the study on VA Greater Los Angeles Facebook, VA Greater Los Angeles Twitter, and the new VA Greater Los Angeles Research and Development website (see attached social media announcements). Patients who are interested in the study will be advised to call the study office to learn more about the study.

If a Veteran calls the study office in response to seeing a flyer, poster, social media announcement, or receiving a flyer from a provider, research staff will follow the protocol described below (see telephone eligibility screening).

| **Table 1. Inclusion and Exclusion Criteria** |
|---|
| **Inclusion criteria:** |

Inclusion and Exclusion Criteria

Table 1 lists the inclusion criteria for the sampling frame and enrollment into the study. We anticipate enrolling up to 600 participants and randomizing 132 to receive the intervention. Exclusion criteria for enrollment and randomization are also listed in Table 1.

| |
|---|
| • Age ≥ 55 years<br>• Use of lorazepam, alprazolam, temazepam, clonazepam, and/or zolpidem for current or prior insomnia symptoms 2 or more nights per week[57;58] for at least 3 months<br>• Current or prior insomnia symptoms<br>• Available to attend weekly in-person or video sessions over 9 weeks |
| **Exclusion criteria:** |
| High risk for complications in outpatient hypnotic discontinuation program:<br>• Seizure disorder<br>• Supratherapeutic/high baseline hypnotic dose (> diazepam-equivalent of 8 mg/night). Note that for individuals on > 1 of the targeted hypnotics, total baseline dose in diazepam-equivalents will be calculated & if > 8 mg/night, individual will be excluded.<br>• High risk of complicated withdrawal; benzodiazepine intoxication or current or past symptoms of complicated benzodiazepine/alcohol withdrawal (e.g., seizure, delirium at baseline)<br>• Polydrug use (e.g., chronic high dose opioids)<br>• Unable to keep study medications in secure location<br>• Evidence of prescription fraud (e.g., multiple prescriptions for same drug filled at VA and non-VA pharmacies, diversion) |
| Discontinuation of hypnotic not appropriate:<br>• Study-targeted hypnotic used to treat another clinical condition (e.g., REM sleep behavior disorder)<br>• Not willing to begin hypnotic discontinuation program |
| Poor candidate for CBTI:<br>• Presence of bipolar disorder<br>• Cognitive impairment (e.g., Mini-Mental State Examination < 24)<br>• Sleep/wake difficulty is better explained by another sleep disorder such as restless legs syndrome, narcolepsy, insufficient sleep syndrome, or circadian rhythm sleep-wake disorders<br>• Untreated sleep-disordered breathing **(**apnea-hypopnea index ≥ 30) Moderate sleep apnea (apnea-hypopnea index between 15-29.99) and daytime sleepiness (Epworth Sleepiness Scale score >10)<br>• Medically/psychiatrically unstable (e.g., recent major hospitalization or planned major surgery during the study; psychosis, suicidal, active alcohol/substance abuse based on history and medical records)<br>• Unstable housing situation |

Recruitment, enrollment

- Recruitment letter

Veterans identified from the CDW database will be mailed a recruitment letter and opt-out card (see Recruitment letter and Opt-out card). Veterans will be asked to return the opt-out card in a postage-paid envelope within 7 days of the letter mail date to indicate whether they wish to be called by our research staff. The letter will explain that research staff will call the Veteran if the opt-out card is not returned within the 7-day timeframe. In total, we plan to send this recruitment package to approximately 2500 older Veterans over the first three years of the study.

We will obtain a revised list from both databases throughout the first 3 years of the study as new names are needed for recruitment. This process will enable us to have a current list of names for our sample. In our previous work, we found that Veterans with a visit in the prior 2 quarters were more likely to have a valid mailing address and to participate in research than Veterans who had not received care in that timeframe.

- Telephone eligibility screening

Study staff will telephone potential participants who were sent the recruitment letter but did not return the "opt out" card. They will also telephone Veterans who were referred to the study by a VA provider. Staff will leave up to 4 telephone messages. Veterans who do not return our call after the 4 messages will be considered as "not interested" in participating.

During this telephone call, the study will be explained and verbal consent for screening will be obtained from Veterans who express interest in the study (see Telephone Screening Script). Additional eligibility criteria will be assessed with a structured screening questionnaire (see Telephone Screening Questionnaire). The screening questionnaire will include items to assess the following: 1) current insomnia symptoms, 2) hypnotic use, 3) number of months and nights per week hypnotic is used, 3) major health events (e.g., surgery) within the past month (individuals with a recent major event will be re-contacted 3 months later), 4) housing situation (e.g. homelessness), 5) access to transportation to the medical center, 6) perceived physical, emotional or substance use being a barrier to participating in the study sessions. The same script and telephone screening questionnaire will be used for Veterans who call the study office in response to the recruitment flyer.

Following completion of the telephone screening questionnaire, eligible and interested Veterans will be scheduled for an initial meeting (in-person or by video) to obtain written informed consent. Potential participants also will be informed that they can receive a blank written informed consent form in the mail to provide them with sufficient time to consider participation and discuss participation with family members, should they so desire.

During the telephone screening, potential participants will also be informed that prior to the consent visit, research staff will review their CPRS medical record to identify hard exclusion criteria, such as clear diagnosis of bipolar disorder, substance abuse, benzodiazepine/z-drug doses that are supratherapeutic, or untreated severe obstructive sleep apnea. Participants who have any of these exclusionary criteria will be informed that they currently do not meet study inclusion/exclusion criteria and the in-person or VVC consent appointment will be cancelled.

- In-person consent visit

When a potential participant comes to the consent visit, a trained research staff member will discuss the study with her/him and answer any questions. Potential participants will be shown the wrist actigraph and FDA-approved, commercially available home sleep apnea testing device (e.g.,WatchPat monitoring equipment) to ensure that they become familiar and comfortable with this equipment. In our ongoing studies, nearly all individuals elect to sign the informed consent form at the time of the in-person meeting. However, Veterans will have the option of taking a blank consent form home to discuss with their family/friends. Capacity to give informed consent will be evaluated with a brief questionnaire (see Evaluation to Sign a Consent Form for Research), previously approved by the IRB, that asks the Veteran to recount major procedures and risks of the study. Veterans who are unable to provide informed consent will be excluded; proxy consent will not be pursued. Participants who are able to provide informed consent will be asked to sign the written informed consent form and HIPAA authorization and will be provided with copies.

**Amendment to recruitment protocol**

We will also recruit UCLA patients. The recruitment methods will differ from those above because they involve patients from a different institution with their own IRB and Compliance Office (Privacy). The recruitment will begin with a query of the UCLA Data Warehouse to identify patients on target medications. Second, potentially eligible patients will be sent a UCLA recruitment letter and opt-in/out form. Patients who do not opt-out will be contacted following a UCLA IRB approved telephone screening protocol. UCLA patients who are eligible and interested in enrolling in the study will be invited to a consent appointment at the VA. At this point forward, all study activities will align with the approved protocols for the current VA study. These UCLA patients will be enrolled as non-Veterans. The informed consent process will be identical to the process described above, except on-Veteran participants will sign a separate consent form that includes a statement that an electronic VA medical record will be established for all non-Veteran participants. They will also sign the VA HIPAA, and VHA Form 10-0483, Acknowledgement of the Notice of Privacy Practices. Non-Veteran participants also will be asked to sign a UCLA HIPAA form, so Dr. Fung and other study staff who have a UCLA appointment, can access the UCLA electronic medical record.

Amendment for telehealth option

The process for obtaining consent by VA Video Connect (VVC) is described below:

1. Research staff will schedule a VVC visit
2. A Virtual Care Manager Ad Hoc Video Visit invitation is auto-generated by VVC and is sent via the Virtual Care Manager interface to the participant
3. Research staff will send participants an email to confirm the appointment and notify them that a VVC email should arrive in their inbox with a link to use to connect to VVC
4. Study materials mailed to participants will include:

- Cover sheet describing content of package
- Informed consent, VA HIPAA form, and if applicable for non-Veterans, a UCLA HIPAA form
- Addressed, postage-paid envelope to return consent/HIPAA forms
- Paper disposable ruler (needed for assessment visit to obtain neck circumference)

VVC Consent Visit

A member of the study team will follow the in-person protocol for obtaining consent, including showing potential participants the wrist actigraph and portable sleep apnea screening device, administering the capacity to give informed consent questionnaire, answering all questions, and observing the participant sign the informed consent and HIPAA forms. Participants will be instructed to mail the signed forms back to a study post office box using the postage-paid return envelope. At the end of the visit, an appointment will be scheduled for the first baseline assessment visit.

Amendment for telephone visit

If video connection is not possible due to technical issues (e.g., bandwidth connectivity issues, software problems, hardware issues), research staff will conduct the consent visit via telephone. The participant will already have received the necessary study materials (i.e., informed consent, HIPAA form, return envelope, paper disposable ruler). Staff will follow the same protocol for obtaining consent as is described above for the VVC visit, with the exception that they will not be able to observe the participant sign the forms.

Baseline Assessment

After participants have provided written informed consent (in-person Visit 1), they will complete a baseline assessment that consists of 2 visits (each 45-60 minutes) to the study site. Participants who complete the baseline assessment will receive $25 for their travel and time. Components of the baseline assessment will include:

- Research assistant administered questionnaires (see Table 2)
- Blood pressure, pulse and respiration
- A wrist actigraph will be given to participants to wear at home for 1 week
- A sleep diary will be given to participants to complete while wearing the actigraph
- Screening for sleep apnea – all participants will be administered the STOP-Bang questionnaire to screen for symptoms of sleep apnea. If a participant scores > 4 on the STOP-Bang and does not have documentation of a previous sleep study in the CPRS medical record, s/he will be sent home with a portable sleep apnea screening device (WatchPAT) to wear for one night. The participant will return the home sleep apnea testing device (e.g., WatchPAT) the next day to the research office.
- Hypnotic medication log - Using a structured hypnotic abstraction form (see Hypnotic Abstraction Form), we will review CPRS to obtain data about VA hypnotic prescriptions. We will also query the California Controlled Substance Utilization Review and Evaluation System (CURES) database to obtain data about prescriptions of controlled substances.

Amendment for telehealth option

During the current pandemic, we have added the option to replace in-person research contacts with remote contacts using the VA Video Connect (VVC) platform. This is the same platform that VA clinicians use for video health visits. Use of the video option will be based on current VA guidelines for in-person visits and participant preferences.

The process for completing the baseline assessment by VVC is described below:

1. Research staff will schedule a VVC visit
2. A Virtual Care Manager Ad Hoc Video Visit invitation is auto-generated by VVC and is sent via the Virtual Care Manager interface to the participant
3. Research staff will send participants an email to confirm the appointment and notify them that a VVC email should arrive in their inbox with a link to use to connect to VVC
4. Participants will be provided instructions for preparing for the baseline assessment (e.g., anticipated duration, equipment/materials needed, staff contact information)

Amendment for telephone option

If video connection is not possible due to technical issues (e.g., bandwidth connectivity issues, software problems, hardware issues), research staff will conduct the baseline visit via telephone.

VVC/Telephone Baseline Visit Procedures

Staff will conduct the 2 baseline assessment visits by VVC/telephone following the same protocol as used during in-person visits, except that the 1-leg balance test will not be performed. Certain items needed for the baseline assessment will be mailed to participants prior to the second baseline visit. These items include:

- Wrist actigraph
- 7-day sleep diary
- Hypnotic medication log
- Paper copies of the Trails, Digit Symbol/Symbol Copy tests
- Sleep apnea screening device (e.g., Watch PAT), if STOP-BANG score > 4
- Postage-paid, pre-addressed, insured delivery box (“Return Delivery” Box)

Participants will also have the option to meet staff at a VA GLAHS facility that is near their home to pick-up and return study devices//materials. In those circumstances, staff will meet the participant in a parking lot or lobby to exchange devices, while maintaining social distancing.

If it is determined that the MINI needs to be administered to a participant, a separate VVC visit will be scheduled.

| **Table 2: Data Collection Instruments** | | | **Time point for data collection** | | | |
|---|---|---|---|---|---|---|
| **Instrument NAME** | **Standard or Study-Specific** | **Purpose** | **Baseline** | **Intervention** | **Post** | **6-months** |
| Self-Administered Comorbidity Questionnaire[15] | Standard | Self-reported medical/psychological conditions | X | | | |
| Insomnia Severity Index (ISI)[16] | Standard | Insomnia symptoms severity | X | X | X | X |
| Pittsburgh Sleep Quality Index (PSQI)[17] | Standard | Self-reported sleep quality | X | ~~X~~ | X | X |
| Dysfunctional Beliefs and Attitudes about Sleep – 16 item (DBAS-16)[18] | Standard | Beliefs about insomnia | X | | X | X |
| Morningness Eveningness Questionnaire (MEQ)[19] | Standard | Circadian rhythm sleep disorders | X | | | ~~X~~ |
| Disturbing Dream/Nightmare Severity Index (DDNSI)[20] | Standard | Frequency and severity of nightmares | X | | X | X |
| Restless Leg Syndrome questionnaire (RLS)[21] | Standard | Symptoms of restless legs syndrome | X | | ~~X~~ | ~~X~~ |
| STOP-Bang questionnaire[22] | Standard | Symptoms of sleep apnea | X | | | |
| Epworth Sleepiness Scale (ESS)[23] | Standard | Daytime sleepiness | X | X | X | X |
| Brief Pain Inventory (BPI)[24] | Standard | Pain assessment | X | | X | X |
| WHO Quality of Life -BREF (WHOQOL-BREF)[25] | Standard | Health-related quality of life | X | | X | X |
| Mini-International Neuropsychiatric Interview (MINI) [26] | Standard | Full interview or partial interview using only the depression, mania, psychosis, and suicidality symptom modules. Only used with participants who have history of bipolar disorder. | X | | | ~~X~~ |
| Primary Care Post-Traumatic Stress Disorder (PC-PTSD) [27] | Standard | PTSD symptoms, exposure | X | | X | X |
| Generalized Anxiety Disorder (GAD-7)[28] | Standard | Anxiety symptoms | X | | X | X |
| Patient Health Questionnaire-Depression Module (PHQ-9)[29] | Standard | Depression symptom severity | X | | X | X |
| Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[30] | Standard | Screens for substance abuse | X | | | |
| Trails A & B tests[31] | Standard | Mental processing speed, attention, executive functioning | X | | X | X |
| Digit Symbol Substitution and Symbol Copy[32] | Standard | Mental processing speed and attention | X | | X | X |
| Mini-Mental State Examination (MMSE)[33] | Standard | Cognitive status | X | | X | X |
| One-leg standing balance[34] | Standard | Balance measurement | X | | X | X |
| Benzodiazepine Dependence Questionnaire (DBEP)[35] | Standard | Symptoms of benzodiazepine dependence | X | | X | X |
| Clinical Institute Withdrawal Assessment Scale – Benzodiazepines (CIWA-B)[36] | Standard | Symptoms of benzodiazepine withdrawal | X | X | X | X |
| Credibility/expectancy questionnaire (CEQ)[37] | Standard | Self-reported confidence in treatment | ~~X~~ | X | ~~X~~ | ~~X~~ |
| Demographic questions | Study-specific (attached) | Characteristics of participants (e.g., marital status, living location, employment) | X | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Fall event question | Study-specific (attached) | History of slips/trips/falls | X | | X | X |
| ICSD-3 questions | Study-specific (attached) | Symptoms of insomnia based on ICSD-3 criteria | X | | X | X |
| Additional comorbidity questions | Study-specific (attached) | Self-reported medical/psychological conditions | X | | | |
| Nighttime urinary symptoms questions | Study-specific (attached) | Frequency and impact of nighttime urination | X | | X | X |
| Hypnotic abstraction form | Study-specific (attached) | Prior and current use of hypnotics | X | | X | X |
| Medication log | Study-specific (attached) | Medications taken during week while wearing wrist actigraph | X | | X | X |
| Sleep diary | Study-specific (attached) | Self-reported daily sleep patterns | X | X | X | X |
| Fall log | Study-specific (attached) | Self-reported daily fall record | | | X | X |
| Treatment arm question | Study-specific (attached) | Self-reported question asking participant which treatment received | | | | X |
| Watch-PAT instruction sheet | Study-specific (attached) | Questions about sleep apnea device use and times associated with Watch-PAT use | X | | | |
| Subject Contact Information sheet | Study-specific (attached) | Updated contact information | | | X | |

Eligibility determination for randomization

The final determination of eligibility will take place during a weekly meeting of the investigators. At least one physician (Fung or Alessi) and at least one sleep psychologist (Martin) will participate at these meetings. During this "pre-randomization review" meeting, individuals who no longer meet the hypnotic criteria at the baseline assessment will be excluded. Individuals adherent to sleep-disordered breathing therapy and restless legs syndrome (RLS) therapy or with insomnia symptoms incompletely explained by RLS will be considered for intervention, as would be done in clinical practice. Individuals with insomnia symptoms due to circadian rhythm sleep disorders or inadequate opportunity for sleep will be excluded.

Participants with an apnea-hypopnea index ≥ 30 (from home sleep apne testing device such as WatchPAT) will not be eligible for randomization. Participants with an apnea-hypopnea index between 15 and 29.99 (moderate sleep apnea) and with daytime sleepiness (Epworth Sleepiness Scale score > 10) will also not be eligible for randomization. Participants with an apnea-hypopnea index between 15 and 29.99 and no daytime sleepiness will be eligible for randomization. We will inform participants with an apnea-hypopnea index > 15 that they may have sleep apnea and, with their permission, will initiate a consult to the VA GLAHS Sleep Center, or inform their primary care provider.

A review of the participant's medical record will be completed to assess for unstable medical or psychiatric conditions (e.g., new chemotherapy) that would make it difficult to maintain the participant's engagement in the study. These individuals would also not be appropriate for CBTI under usual care conditions. Individuals excluded for unstable conditions will be reassessed 3 months later for eligibility, which is the process that would occur in a clinical setting. We will include individuals with stable psychiatric or medical conditions such as chronic pain or depression. Finally, we will notify the participant's hypnotic prescriber at VAGLA or the participant's non-VA provider (via encrypted email) about our intention to taper and discontinue the patient's hypnotic in case there are undocumented clinical indications other than insomnia (see Email to Prescribers). If the prescribing physician does not agree with tapering the medication, the individual will not be randomized. Participants determined to be ineligible for the study will be notified by mail (see Participant Ineligibility Letter).

Randomization

Individuals who complete the baseline assessment and meet all inclusion/exclusion criteria will be randomly assigned to one of the two intervention groups: MTcap (N=66) or SGT+CBTI (N=66). Both interventions are described below. Randomization procedures will follow the CONSORT criteria for randomized trials. Stratified

randomization will be used to ensure that both groups are balanced in baseline hypnotic drug type half-life (i.e., temazepam/zolpidem; alprazolam/lorazepam; clonazepam) and gender. The study statistician will generate the stratified randomization sequence. A set of envelopes containing the group assignment will be generated and stored in a secure file drawer accessible only authorized staff. Once final eligibility is determined, the data manager will open the next envelope in sequence within the appropriate stratum.

Interventions

Both interventions will involve 8 sessions provided by a trained cognitive behavioral therapy for insomnia (CBTI) interventionist. The intervention period is expected to last approximately 9 weeks (but may be extended as described below). Both interventions include a tapering protocol for benzodiazepine use, behavioral therapy for insomnia, plus weekly assessment for withdrawal symptoms. During week 7 and at the beginning of week 9 of the intervention, participants will only receive the withdrawal symptom assessment (see table to right). Participants will receive $25 for attending the 2 withdrawal symptom assessments. The actual content and structure of the behavioral therapy and tapering protocol will differ between the two groups, although the dose reduction schedule will be the same for the two groups (described below). Intervention sessions will take place in designated, private research offices at VAGLA. All interventionist sessions will be audio-recorded and a random subset will be rated using a structured rating sheet to ensure fidelity to the treatment protocol. The interventionist will also maintain a session-by-session list of information covered and recommendations made. "Progress notes" will be maintained by the interventionist and reviewed during weekly "intervention meetings." These processes will ensure fidelity over the course of the study and avoid the risk of contamination across study arms.

| Week | Session | MTcap Group | SGT+CBTI Group |
|---|---|---|---|
| 1 | 1 | Intervention + BWA | Intervention + BWA |
| 2 | 2 | Intervention + BWA | Intervention + BWA |
| 3 | 3 | Intervention + BWA | Intervention + BWA |
| 4 | 4 | Intervention + BWA | Intervention + BWA |
| 5 | 5 | Intervention + BWA | Intervention + BWA |
| 6 | 6 | Intervention + BWA | Intervention + BWA |
| 7 | | BWA only | BWA only |
| 8 | 7 | Intervention + BWA | Intervention + BWA |
| 9 Beginning of week | | BWA only | BWA only |
| 9 End of week | 8 | Intervention + BWA | Intervention + BWA |

BWA=Benzodiazepine withdrawal assessment (i.e., CIBA-B, vitals, ISI, ESS)

Amendment for telehealth option

Intervention sessions conducted by VVC

Participants who receive the intervention sessions by VVC will receive the auto-generated and study-generated emails described above for the baseline assessments. The content of the intervention and taper schedules used to taper hypnotic use will be identical to the in-person sessions.

Prior to the first intervention session, the following materials will be mailed to participants:

- Notebook containing education materials for each session
- Sleep diaries for each week
- Blood pressure machine (if participant does not have a blood pressure machine at their home)
- Questionnaires (i.e., CIWA, ISI, ESS questionnaires) completed at sessions
- Postage-paid, self-addressed return envelopes to return questionnaires
- Medication for SGT group: 30-day supply plus Paper Taper Schedule in a sealed envelope to be opened at Session 1
- Medication for MTcap group: 3-week supply plus 3 weeks PRN plateau
- Postage-paid, pre-addressed, delivery box to return unused medication.

Additional medication will be mailed to participants over the course of the intervention according to the taper schedule for that group.

Amendment for telephone option

If video connection is not possible due to technical issues (e.g., bandwidth connectivity issues, software problems, hardware issues) research staff will conduct the intervention session via telephone. Staff will follow the same protocol as described for VVC visits.

- Measures collected during intervention:

*A urine sample* will be collected from participants at the first intervention session. The urine sample will be tested for benzodiazepines and zolpidem to confirm the participant's use/nonuse of these hypnotics.
The following measures will be collected weekly throughout the intervention for participants in both study groups.
*Clinical Institute Withdrawal Assessment Scale - Benzodiazepines (CIWA-B):* This 22-item instrument includes patient symptoms and clinical observations (e.g., tremor) to assess and monitor the type and severity of symptoms of benzodiazepine withdrawal.
*Vital signs:* These physical examination measurements will be taken weekly: blood pressure, pulse, respiratory rate.
*Insomnia Severity Index (ISI):* The ISI is a 7-item instrument that measures perceived severity of insomnia symptoms (total score ranges from 0 to 28).
*Epworth Sleepiness Scale (ESS):* This 8-item questionnaire assesses general level of daytime sleepiness.

Amendment for telehealth option
Urine sample: Participants who receive the intervention by VVC/telephone will be asked to go to the VA clinical lab to provide a urine sample prior to the first intervention session.
Vital signs: The interventionist will assess respiratory rate and observe the participant measure their blood pressure and pulse via VVC at each session.

Daily sleep and habits diary: Participants will use the diary to record bedtime, wake time, total sleep time, time to fall asleep, time awake at night, number of awakenings, napping, exercise, alcohol use. Participants in the MTcap group only will also record their perceived hypnotic dose taken and their daytime function and sleep quality.

- MTcap (Masked Taper plus cognitive behavioral therapy-augmented program):
  ~~a.~~ Hypnotic taper protocol: Participants will receive encapsulated hypnotics in a blister taper pack prepared by a non-VA compounding pharmacy. Participants will be informed that gradual dose reduction will occur during the program, but they will be blinded to the actual dose they receive each day. The planned rate of reduction of hypnotic will be about 25% per week. The final taper pack will consist of 4 placebo capsules (nights 1-4) and 3 empty blisters (nights 5-7). This planned rate of taper would yield a taper length similar to those reported in other studies, where the average length of taper was 49 days (range 6.5 to 84 days).

  b. Cognitive behavioral therapy for insomnia-augmented program: The 8 sessions will incorporate the key components of CBTI (sleep restriction, stimulus control, cognitive restructuring, targeted sleep hygiene) and CBT targeting hypnotic withdrawal. Using the masked doses as a CBT tool, we will add exercises and concepts designed to address and alter expectations for hypnotics. A daily sleep/perceived hypnotic dose diary will be used as a tool for challenging expectancies about hypnotics, refining treatment recommendations, and adjusting the weekly plan.

- SGT+CBTI:
  a. Hypnotic taper protocol: Participants will receive hypnotics in a traditional medication container prepared by a non-VA compounding pharmacy. Participants will also receive a printed taper schedule (see attached Taper Schedule) that reduces the hypnotic using the same schedule as the MTcap group. Each participant will be given a pill cutter so they can cut pills in half or into quarters as directed. A printed taper schedule is routinely used in VA clinical practice to assist patients in reducing hypnotic use. An exception to this protocol will occur if the prescribed medication is temazepam. This medication only comes in capsule form, so it cannot be cut into halves or quarters. Consequently, the participant will receive two difference strengths of temazepam (e.g., 15mg and 7.5mg) in two separately labeled bottles. Rather than cutting the higher strength capsule in half, participants will take the lower strength capsule. This is the taper method that is used clinically for temazepam.

  b. Cognitive behavioral therapy for insomnia: Participants will receive standard CBTI (i.e., stimulus control, sleep restriction, targeting maladaptive beliefs about sleep, sleep hygiene, and relaxation techniques),

and will not be provided with the extra exercises and tools that the MTcap group will receive. The sleep diary that participants will complete will be slightly different from the MTcap sleep diary.

- Extended taper plan
  We have identified specific situations when the taper plan may need to be modified:
  a. Withdrawal symptoms/extended taper required: The taper may be extended up to a maximum of 16 weeks if the participant has withdrawal symptoms or cannot tolerate the scheduled taper, based upon changes in several of the CIWA-B items and vital signs, along with the patient's, interventionist's, and study physicians' judgments. In the MTcap group, an extended taper may be achieved by giving a duplicate 7-day blister pack (e.g., plateauing the doses until the participant is ready to move to the next blister pack). In the SGT+CBTI group, participants will be instructed to repeat a particular week in the printed taper schedule. Participants will continue to be monitored with weekly CIWA-B, vital signs, and the interventionist will review and reinforce key content of the intervention.
  b. Hypnotic dosed as "prn" at baseline: Taper schedules for participants who used their hypnotic "as needed" at baseline will be adjusted so that the starting week's total weekly hypnotic dose does not exceed the participants' total weekly baseline hypnotic dose.

     For the MTcap group, the capsules on the predetermined drug-free days will be filled with an inert filler substance. The participants will still be instructed to take the capsule on a scheduled based nightly, not as needed. The use of capsules will ensure that the participant is not exposed to the drug more frequently than the baseline exposure. An increase in adherence to the taper protocol is one rationale for using capsules filled with inert filler substance rather than instructing participants not to take any capsule at all (i.e., similar to oral contraceptive inert pills that are provided in the monthly oral contraceptive pill pack). Another rationale for using insert capsules is related to our study's objective, which aims to develop an intervention for reducing placebo effects, such as the effects related to the conditioned response of taking the drug and attributing sleep and daytime function—which are known to vary from day to day—to the act of taking the pill.

     For the SGT+CBTI (supervised gradual taper + CBTI) group, the paper taper schedule will indicate which days of the week the participant should and should not take the hypnotic. For example, Mondays, Wednesdays, Fridays, and Saturdays may be deemed drug days, while Tuesdays, Thursdays, and Sundays may be deemed drug-free days. The gradual tapering of drug doses on the drug days will occur over the two-month period. The drug-free days will be clearly marked on the taper schedule. A progressive increase in the number of drug-free days will occur during the taper.

  c. More than 1 hypnotic at baseline: Participants who use >1 of the target hypnotics will be tapered off the targeted hypnotics simultaneously using two different blister packs.

- Procotols for preparation of hypnotics

  MTcap group: The blister packs containing the hypnotic will be prepared by Lynn Oaks Compounding Pharmacy located in Thousand Oaks, California, which has staff that are experienced in preparing medications for research purposes. Dr. Fung will write prescriptions for the appropriate hypnotic that will cover the entire intervention period. The prescriptions will be sent via encrypted email or fax to the pharmacy. The compounding pharmacy will prepare the blister packs for the intervention period (e.g., 8 weeks, but could be longer if the participant needs a prolonged taper) and send them via overnight mail or courier to the VA Research Pharmacy. If necessary, the medications will be picked up by research staff and transported to the Research Pharmacy. The research pharmacist will label the blister packs per VA protocols. The prescription will be entered into CPRS as a non-VA prescription.

  SGT+CBTI group: Dr. Fung will write prescriptions for the appropriate hypnotic that will cover the entire intervention period. The prescriptions will be sent via encrypted email or fax to the pharmacy. The compounding pharmacy will prepare a 30-day supply of the appropriate medication for the participant. The medication will be dispensed in a regular prescription bottle and labeled by the pharmacy. At the end of the month, a second 30-day supply of medication will be prepared and dispensed. The medication will be sent via overnight mail or courier to the VA Research Pharmacy. If necessary, the medications will be picked up by research staff and transported to the Research Pharmacy. The prescription will be entered into CPRS as a non-VA prescription.

- Protocols for distribution of hypnotics
  For both groups, a member of the research team will pick-up the medication bottle or blister packs from the VA Research Pharmacy and give it to the participant at the first intervention session. If the participant does not come to the appointment, the medication will be returned to the Research Pharmacy. If the Research Pharmacy is closed (e.g., the pharmacist has left for the day, is at a meeting), the medication will be stored either in a locked safe (located in Building 115, Room 328) or the locked narcotics box in the Clinical Research Center (CRC) in Building 500 on the West Los Angeles campus until the Pharmacy reopens or it can be given to the participant.

  For participants seen on the Sepulveda campus, a research team member will transport the medication via personal car to Sepulveda. The medication will be placed in a locked bag and stored in the trunk during transport. The medication will be stored in a locked safe in Building 25/Room A137 until the participant receives it at the first session. If the participant does not come to the appointment, the medication will be returned to the safe.

Amendment for telehealth option

Medications will be mailed to participants following the same procedures used by the VA pharmacy service. Participants will also have the option of picking up the medication from our research staff at the Sepulveda VA or West Los Angeles Medical Center.

- Care coordination at end of intervention period
  Participants in the MTcap group will be told the benzodiazepine dose that they are taking when they complete the intervention (or if they withdraw before the 9-week intervention period). The primary care providers of participants in both groups will be informed of the final medication regimen, so patients can continue to be monitored for withdrawal, if necessary.

  At the last session of the intervention, the interventionist will use a debriefing script (see attached Debriefing Script) to inform MTcap participants of the actual doses that they were taking over the 9-week intervention. Participants will be given the taper schedule that the SGT+CBTI group followed (see attached Taper Schedule) unless there was a plateau in the tapering, in which case participants will be shown a revised taper schedule. The interventionist will tell participants the dose that they are currently taking and will review the last week's sleep diary to compare what participants thought they were taking with the actual dose. Participants will be given an opportunity to ask questions about the research, will be asked if they agree to allow the investigator to use the data collected up to that point in the study (additional data will be collected at post-treatment, and 6-months), and will be given contact information for the interventionist and Dr. Fung.

<u>Follow-up assessments</u>

We will encourage participants to complete assessments even if they elect not to complete the intervention. All follow-up assessments will be conducted by research staff who are blinded to group assignment.

- Post-treatment assessment

The post-treatment assessment will begin on the same day that the participant completes session 8 of either intervention. At the end of session 8, a participant will be provided with an actigraph to wear at home for 1 week and a sleep and medication diary to complete. When the participant returns the actigraph and diary after 1 week, he/she will be administered selected questionnaires included in the baseline assessment. In addition, a urine sample will be collected to confirm participants' self-report of hypnotic discontinuation. Participants will also be given a six-month fall log to record any falls they experience during the period between the post-assessment and the six-month follow-up assessment. The CURES database will also be queried to obtain data about prescriptions for controlled medications. Participants who complete the post-treatment assessment will receive $50 for their travel and time.

- Six-month follow-up

The six-month assessment will occur six-months after session 8 is completed (or was scheduled to be completed if a participant drops out of the intervention). This assessment will include 2 visits to the study site.

The measures collected will be identical to the post-treatment assessment. At visit 1, the participant will receive an actigraph to wear at home for 1 week, a sleep and medication diary to complete, and selected questionnaires will be administered. At visit 2, the participant will return the actigraph, diary, six-month fall log, and will complete additional questionnaires and provide a urine sample. The CURES database will also be queried to obtain data about prescriptions for controlled medications. Participants who complete the 6-month follow-up will receive $50 for their travel and time.

Amendment for telehealth option
Post-treatment follow-up assessment (begins at end of session 8)
Prior to intervention session 8 VVC visit, participants will receive by mail/pick-up the following items:

- Wrist actigraph
- Sleep diary
- Questionnaire packet
- Medication log
- Fall log
- Postage-paid return, insured Return Box to return the study materials (e.g.,actigraph)

Participants will also be instructed to go to the VA clinical laboratory to provide a urine sample.

At the end of session 8, the participant will be instructed to put on the actigraph to wear at home for 1 week and to complete the sleep and medication diary each day of that week.
One week later, a VVC post-treatment assessment visit will occur. At that visit, the participant will be administered selected questionnaires included in the baseline assessment. Participants will also be instructed to record any falls they experience over the next six months in the fall log. Participants will mail/deliver the actigraph and sleep diary back to the study office.

Six-month follow-up assessment
A few days prior to the VVC visit, participants will receive by mail/pick-up the following items:

- Wrist actigraph
- Sleep diary
- Questionnaire packet
- Medication log
- Postage-paid return, insured Return Box to return the study materials (e.g., actigraph, sleep diary and fall log)

Participants will also be instructed to go to the VA clinical laboratory to provide a urine sample.

Participants will wear the actigraph for 7 days and nights, complete the sleep diary, and answer the questionnaires over the course of two VVC visits.

Amendment for telephone option
If video connection is not possible due to technical issues (e.g., bandwidth connectivity issues, software problems, hardware issues), research staff will conduct the follow-up visits via telephone.

Amendment for abbreviated mailed follow-up questionnaire
When a participant is unable to be contacted (e.g., due to a non-working phone number) or refuses to complete a follow-up assessment by video or telephone, the participant will be mailed an abbreviated assessment that includes three questionnaires from the approved follow-up assessment (i.e., ISI, Dbase-16, and sleeping pill use).

Amendment to add giftcards as an alternative patient compensation
The giftcards will serve as alternative subject payment if the subject did not receive original VA issued check compensation after a completed study visit. This addition to the protocol was added to reduce delayed payment compensation and maintain study integrity.

- Follow-up for Missed Appointments

Participants who miss a study appointment will be telephoned by research staff on the day of the missed appointment. If the participant does not return the call within 10 days of the missed appointment, a letter will be sent that encourages the participant to contact the research office (see Missed Appointment Letter). If a participant has not returned an actigraph or Watch-PAT device, the letter will also include a paragraph about the importance of returning the device. If the participant does not return the device after 10 days from the date of the first letter, a second letter will be sent that explains that failure to return the device requires staff to submit a missing equipment report to VA police (see Failure to Return Device Letter).

Potential Risks and Safety Plan

- Benzodiazepine withdrawal symptoms: Symptoms are not common with withdrawal of low doses of benzodiazepines, but could include dizziness, anxiety, depression, and insomnia. The proposed intervention has a similar risk level to behavioral/ pharmacological strategies recommended by healthcare providers to adults as part of routine clinical care. Based on our pilot data and our team's collective clinical experience with low-dose hypnotic discontinuation, withdrawal symptoms that warrant protocol changes are uncommon. To reduce the risk of severe withdrawal symptoms, adults at high risk of complicated withdrawal or on high benzodiazepine doses (based on comorbidities, current prescriptions, and answers to assessment questions) will not be randomized to receive the intervention. Participants will be monitored weekly with the Clinical Institute Withdrawal Assessment-Benzodiazepine [CIWA-B] instrument and with weekly vital signs. If the participant is found to have mild symptoms of withdrawal based on select items from the CIWA-B or on mild changes in vital signs, a study physician (e.g., Drs. Fung or Alessi) and the participant may decide to plateau the taper until the participant is ready to continue with the dose taper. If participants are found to have moderate, severe, or very severe scores on select items in the CIWA-B, ~~or~~ moderate or severe vital sign changes, or have worsening severed insomnia, the study physicians will discuss the patient's symptoms with a staff psychiatrist to determine whether the changes to the taper schedule are needed (including increasing or plateauing the dose) and whether the patient needs additional clinical evaluation. If the patient needs clinical evaluation, the participant will be escorted to the outpatient clinic or for life-threatening emergencies at our facility, we will call 911.

Amendment for telehealth option

If a participant needs clinical evaluation during a VVC appointment, staff will advise the participant to seek medical care locally at the nearest emergency department, or for life-threatening emergencies, we will call 911.

- Confusion about duplicate hypnotic prescriptions: Participants may not understand that the hypnotic provided by the study (in blister packs or medication bottle) replaces the hypnotic that they were previously taking. This could result in participants taking both prescriptions at the same time, which would result in a higher dose than prescribed, and possible side-effects (e.g., daytime sleepiness, dizziness). To avoid confusion about duplicate hypnotic prescriptions, participants in both groups will be asked to bring all their medications to the first intervention session. The interventionist will identify the hypnotic that will be tapered and will place the bottle in a sealed envelope. A label will be affixed to the outside of the envelope that states, "Do not take this medication during the 8-week SWITCH study unless instructed by the study staff." The interventionist will explain that the participant will receive the same hypnotic either in a new medication bottle or in the blister packs and should put the old prescription in the sealed envelope in a safe location.

- Increased daytime sleepiness: Adjustments to the participant's sleep habits may result in some initial daytime sleepiness. Daytime sleepiness will be monitored during each weekly in-person intervention assessment with the Epworth Sleepiness Scale, and participants with increased daytime sleepiness will be counseled on the possibility of impaired cognition and increased fall and motor vehicle crash risk. If excessive daytime sleepiness is thought to be due to study-related sleep restriction (as opposed to, for example, a newly-prescribed medication from the individual's physician), the prescribed sleep schedule will be adjusted.

- Mental discomfort: The minor risks associated with completion of the questionnaires include tediousness, fatigue, and/or mental discomfort answering the items. Participants could also find wearing the actigraph

and home sleep apnea testing device (e.g., WatchPAT device) to be annoying or uncomfortable. To reduce the risk of mental discomfort among participants, research staff will be trained to recognize discomfort in participants, and they will be trained to remind participants of the voluntary nature of the research and the option for participants to decline participation in any portion of the research project.

- Falling during one-leg balance test: Participants could lose balance and fall during the one-leg balance test. To reduce the risk of falling during the one-leg balance test, research staff will place a gait belt around participants. For participants who use mobility aids, two research staff will perform the testing and additional steps such as placing a walker around the participant may also be employed.

- Skin irritation: The sensors worn for one night as part of the home sleep apnea testing device (e.g., WatchPAT device) and the actigraph wrist band worn for 7 days may cause skin irritation or an allergy. We have extensive experience using wrist actigraphy and the home sleep apnea testing devices such as the WatchPat system, and have chosen these devices because they are well-tolerated by participants. They are also substantially less burdensome than other objective methods of recording sleep (i.e., requiring the participant to spend a night in a sleep laboratory). Research staff will carefully review with participants potential skin problems associated with wearing the wrist actigraph and the home sleep apnea testing device sensors. Participants will be told to remove the device if they have any significant discomfort or any evidence of skin injury. Participants will have access to a research staff person, in case they have questions or concerns about the equipment. In addition, the company which makes the WatchPAT device has a 24-hour advice line that also provides troubleshooting support. Our monitoring devices are checked regularly to insure safe and proper operation. Dr. Fung (PI) will be notified immediately of any significant discomfort experienced by study participants.

- Confidentiality and privacy breach: There is risk of breach of privacy via unintentional disclosure of Protected Health Information, which could lead to embarrassment and fraud, which in turn could have negative financial impact on participants. To ensure confidentiality of the research data collected, all participants will have a unique identification number assigned that is not based on any identifying information. This identification number will be used for all computer databases, which will be stored behind a firewall on the VAGLA Health Services Research & Development (HSR&D)-managed server, as well as for hard copy data collection forms. Access to these databases and hard copy forms will be limited to the study's approved research staff and will not be transmitted. Research hypnotic tracking logs (that use subject identification numbers) will be maintained to ensure that all hypnotics that are prepared, dispensed, and disposed (if unused) are accounted for at all times. These hypnotic tracking logs will be shared with the VA research pharmacy (via a shared folder located behind a firewall). Consent forms and hard copies of data forms will be stored in locked file cabinets in locked offices with access limited to approved research staff, in the VAGLA Geriatric Research, Education and Clinical Center (GRECC) research offices. Electronic lists of names and contact information will be kept separate from other data in limited access folders on the VAGLA HSR&D-managed secure server behind a VA firewall. Data will be destroyed according to the Records Control Schedule.

Amendment for telehealth option

Video/telehealth Standard Practices

VA Video Connect (VVC) will be the preferred platform that will be used for video interactions with research participants. In the event that VVC fails, we will follow current VA guidance and use currently approved patient-facing platforms.

We will use standard video/telehealth practices including verifying the participant's identity, inquiring whether they have privacy during the visit, as well as obtaining their location and an emergency contact, in case of an emergency during the visit.

Our overall procedure for monitoring and reporting study-related adverse events includes:

Step 1: If a participant reports or monitoring reveals a study-related adverse event, research staff will report this to the Principal Investigator (Dr. Fung). When Dr. Fung is unavailable, Dr. Alessi (study co-investigator) will be contacted. The research staff will closely adhere to VAGLA emergency reporting policies and procedures.

Step 2: If indicated, Dr. Fung will speak with the participant to determine the severity and likely cause of the concern. If medical examination is needed and the situation is non-emergent, the participant will be advised to go to the VA outpatient clinic.
Step 3: Dr. Fung will report the event to the IRB and will make a determination whether study protocols should be modified for that participant, whether the participant should be withdrawn from the study, or whether the study protocols should be modified overall.
Step 4: All concerns reported by research staff will be documented, whether they appear to be study-related, and will be reviewed monthly by Dr. Fung.
If a participant reports a high level of mental distress, or discloses suicidal ideation during the interview process, research staff will follow these steps:
Step 1: Research staff will immediately contact Dr. Fung (or another immediately available clinician) who will do an assessment. If relevant, the participant will be provided with the telephone number for the VHA suicide prevention hotline or other local suicide prevention resources.
Step 2: If needed, the participant will be taken by research staff to the mental health or primary care outpatient clinic for evaluation and/or treatment. For all life-threatening emergencies at our facility, we call 911 and notify VA police.
Step 3: As above, events will be reported to the IRB and a determination will be made about the protocol and the appropriateness of the participant continuing in the study.

Primary Analysis Plan

We plan to randomize 132 individuals, of whom we expect 13% to drop out (i.e., fail to complete assessments) by 6-months, yielding N=114 participants with complete data (~ 57 per group). We base this drop-out on our completed study (Alessi VA Merit 08-295). We will include terms for stratification characteristics and covariates for baseline pain intensity, PHQ-9, and opioid use in all of the models. All analyses below assume $\alpha$=0.05, power=0.80, two-sided hypothesis tests, and intention-to-treat approach. Effect sizes are in the measure's natural units and Cohen's *d* (large=.8; medium=.5; small=.2).

- (H1a) Participants who receive MTcap will have increased likelihood of hypnotic discontinuation post-treatment and at 6 months follow-up compared with those who receive SGT+CBTI: Hypnotic discontinuation (yes=1/no=0) will be regressed on treatment group assignment (MTcap vs. SGT+CBTI) in two logistic regression models (post-treatment and 6 months follow-up). Sample size calculations establish that 114 participants will be adequate to detect a difference of 21% to 26% between the MTcap and SGT+CBTI groups, depending upon the discontinuation percentage of the SGT+CBTI group (59% to 63% at follow-up[57;102] in prior studies). In our feasibility study, 100% discontinued hypnotics post-treatment. We will use multiple imputation.
- (H1b) Participants who receive MTcap will use less hypnotic medication post-treatment and at 6 months follow-up compared with those who receive SGT+CBTI: Two outcomes will be assessed: frequency (i.e., 0 to 7 days used) and quantity (i.e., average daily dose in diazepam milligram equivalents[66]). For each outcome, we will fit a 2 (group) by 3 (time) general linear mixed model.[66] Interaction terms will be used to assess the change in the outcome (baseline→post-treatment, baseline→6 months) for MTcap vs. SGT+CBTI. Power Analysis: We use statistics from our recent study, which found a baseline to 6-month correlation of *r*=0.83 (95% CI=0.77-0.88) and a standard deviation (SD) of 1.94 for a similar outcome measure—"days used of medications commonly used for insomnia" (0 to 7 days used). Assuming r=0.83 and n=57 per group, we could detect a treatment effect of 0.60 (Cohen's *d*=0.30) (i.e. a difference of 6/10$^{ths}$ of a day between the groups). Assuming *r*=0.77 (i.e., using the LCL), we could detect a treatment effect of 0.70 days (Cohen's *d*=0.36). If we disregard data from our recent study, power calculations still show that we could detect a treatment effect of 1.02 days (Cohen's *d*=.53; i.e., detect a difference of 1 day between groups). For quantity of use, power calculations indicate that we could detect a treatment effect of *d*=.53 (medium effect).
- (H2) Participants who receive MTcap will have lower Insomnia Severity Index scores at 6 months follow-up compared to SGT+CBTI: We will fit a general linear mixed model, and an interaction term will assess the change in ISI from baseline to 6 months for MTcap vs. SGT+CBTI. Power Analysis: Our prior research shows an ISI SD=5.3 and *r*=0.39 (95% CI=0.24-0.52) between baseline ISI and 6 month follow-up ISI. Assuming this correlation and a sample size of N=57 per group, the study could detect an effect as small as 3.1 units on the ISI (or a Cohen's *d*=.58). Assuming *r*=0.24 (i.e., using the LCL), we could detect an effect as small as 3.43 units on the ISI (or a Cohen's *d*=.65). An effect of 4.0 units on the ISI has been

determined to be clinically-meaningful in prior research,[103] which means that the proposed study would be able to detect effects that are clinically-meaningful (as well as effects that smaller than clinically-meaningful); both of these power analyses suggest that the study could detect effects that are between medium and large effects.

- (H3) Dysfunctional Beliefs and Attitudes About Sleep (DBAS) – Medication Scale ratings will improve compared to SGT+CBTI post-treatment and at 6 months follow-up: We will fit a 2 (group) by 3 (time) general linear mixed model. Interaction terms will be used to assess the change in DBAS medication items (baseline→post-treatment, baseline→6 months) for MTcap vs. SGT+CBTI group. Power Analysis: Our prior research shows a DBAS-16 SD= 2.1 and *r*=0.55 (95% CI=0.39,0.64) between baseline DBAS and 6-month follow-up DBAS. Assuming this correlation and a sample size of N=57 per group, the study could detect an effect size of *d*=0.50, which is a difference of 1.1 units on the DBAS-16. Assuming *r*=0.39 (the LCL), we could detect an effect size of *d*=.58, corresponding to a 1.2 unit change.

Secondary Analysis Plan (H4)

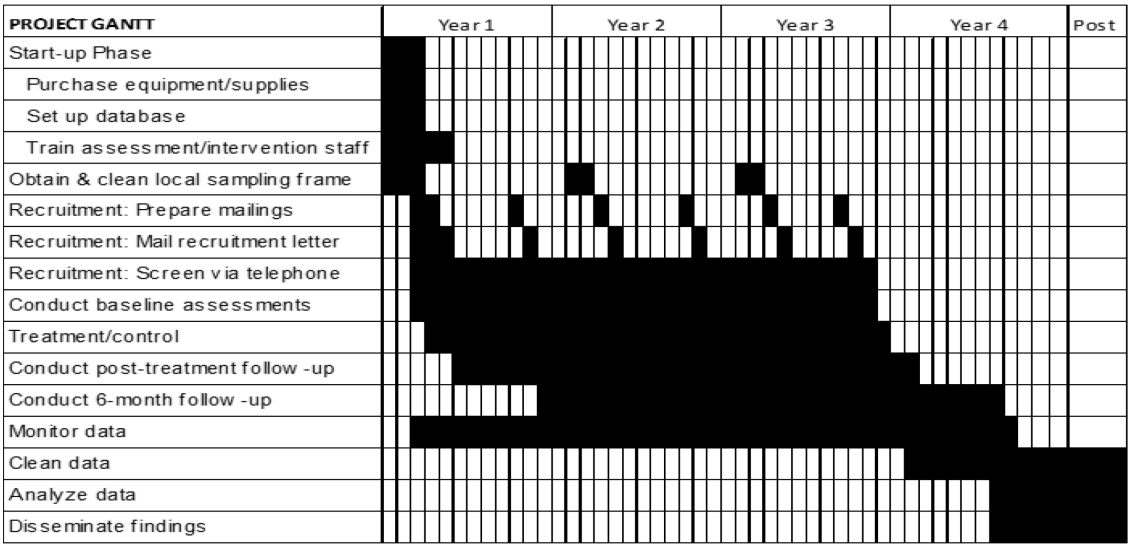
We will test whether MTcap improves cognition (DSS, Symbol Copy; Trails A & B) and balance (One-leg balance) at post-treatment and 6-month follow-up, using general linear mixed model (see Hypothesis 3 above). Effect size calculations: For the most pessimistic case—no correlation between these measures at the two time points—a post-test only analysis could detect a difference of *d*=0.52.

Exploratory Analysis Plan (E1)

We will describe the frequency of falls in each arm. We will test whether MTcap is associated with not falling, using logistic regression (dependent variable [DV] is fall [binary]), which will be predicted as a function of treatment group assignment. E2: Mediation analyses to elucidate the relationship between insomnia severity, hypnotic use, and balance will be conducted using a statistical macro developed by UCLA, which simultaneously tests for the associations of the independent variable (IV; ISI) on the DV (balance), IV on the mediator (hypnotic dose in diazepam equivalents), and IV (ISI) plus mediator (hypnotic dose) on DV (balance) (Sobel, Goodman, and Goodman II tests). Similar mediation analyses (using a Stata user written command for binary mediation) will be performed for the DV, history of fall.

Amendment: We will conduct the same analyses above, but with the addition of data from participants recruited and seen at the UCLA Health site. These data will be transferred in a limited data set from UCLA Health to VA Greater Los Angeles under an approved data use agreement.

## Project Timeline



**References**


3. Ford ES, Wheaton AG, Cunningham TJ et al. Trends in outpatient visits for insomnia, sleep apnea, and prescriptions for sleep medications among US adults: findings from the National Ambulatory Medical Care survey 1999-2010. *Sleep* 2014;37:1283-1293.PMC4096197
4. Mustafa M, Erokwu N, Ebose I et al. Sleep problems and the risk for sleep disorders in an outpatient veteran population. *Sleep Breath* 2005;9:57-63.
5. Rossat A, Fantino B, Bongue B et al. Association between benzodiazepines and recurrent falls: a cross-sectional elderly population-based study. *J Nutr Health Aging* 2011;15:72-77.
6. Allain H, Bentue-Ferrer D, Polard E et al. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. *Drugs Aging* 2005;22:749-765.
7. Zhong G, Wang Y, Zhang Y et al. Association between Benzodiazepine Use and Dementia: A Meta-Analysis. *PLoS One* 2015;10:e0127836.PMC4446315
8. Tsunoda K, Uchida H, Suzuki T et al. Effects of discontinuing benzodiazepine-derivative hypnotics on postural sway and cognitive functions in the elderly. *Int J Geriatr Psychiatry* 2010;25:1259-1265.
9. Barker MJ, Greenwood KM, Jackson M et al. Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: a meta-analysis. *Arch Clin Neuropsychol* 2004;19:437-454.
10. Darker CD, Sweeney BP, Barry JM et al. Psychosocial interventions for benzodiazepine harmful use, abuse or dependence. *Cochrane Database Syst Rev* 2015;5:CD009652.
11. Vicens C, Fiol F, Llobera J et al. Withdrawal from long-term benzodiazepine use: randomised trial in family practice. *Br J Gen Pract* 2006;56:958-963.PMC1934057
12. Perlis ML, McCall WV, Jungquist CR et al. Placebo effects in primary insomnia. *Sleep Med Rev* 2005;9:381-389.
13. Winkler A, Rief W. Effect of Placebo Conditions on Polysomnographic Parameters in Primary Insomnia: A Meta-Analysis. *Sleep* 2015;38:925-931.PMC4434559
14. Perlis M, Grandner M, Zee J et al. Durability of treatment response to zolpidem with three different maintenance regimens: a preliminary study. *Sleep Med* 2015;16:1160-1168.PMC4709332
15. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis & Rheumatism* 2003;49:156-163.
16. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001;2:297-307.
17. Buysse DJ, Reynolds CFI, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213.
18. Morin CM, Vallieres A, Ivers H. Dysfunctional beliefs and attitudes about sleep (DBAS): validation of a brief version (DBAS-16). Sleep 2007;30:1547-1554.
19. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol* 1976;4:97-110.
20. Krakow B. Nightmare complaints in treatment-seeking patients in clinical sleep medicine settings. *Sleep* 2006;2:1313-1319.
21. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir J. Restless legs syndrome: diagnostic criteria, special considerations and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 2003;4:101-119.
22. Silva GE; Vana KD; Goodwin JL; Sherrill DL; Quan SF. Identification of patients with sleep disordered breathing: comparing the Four-Variable screening tool, STOP, STOPBang, and Epworth Sleepiness Scales. J Clin Sleep Med 2011;7(5):467-472.
23. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.
24. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 2004;20:309-318.
25. Skevington SM, Lotfy M, Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL Group. Quality of Life Research, 2004; 13:299–310.
26. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;20:22-23.

27. Cameron, R. P., & Gusman, D. (2003). The primary care PTSD screen (PC-PTSD): development and operating characteristics. Primary Care Psychiatry, 9(1), 9-14.
28. Spitzer RL, Kroenke K, Williams JB et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-1097.
29. Kroenke K, Spitzer RL, Williams JBW. Validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606-613.
30. Humeniuk, R., Ali, R., World Health Organization, & ASSIST Phase II Study Group. (2006). Validation of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and pilot brief intervention [electronic resource]: A technical report of phase II findings of the WHO ASSIST Project.
31. Reitan RM. Trail Making Test: Manual for Administration and Scoring. Tucson, Arizona: Reitan Neuropsychology Lab, 1992.
32. Joy S, Kaplan E, Fein D. Speed and memory in the WAIS-III Digit Symbol--Coding subtest across the adult lifespan. Arch Clin Neuropsychol 2004;19:759-767.
33. Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). Psychopharmacol Bull. 1988;24(4):689-92
34. Michikawa T, Nishiwaki Y, Takebayashi T et al. One-leg standing test for elderly populations. J Orthop Sci 2009;14:675-685.DBEP
35. Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. J Clin Psychopharmacol 1989;9:412-416.
36. Baillie AJ, Mattick RP. The benzodiazepine dependence questionnaire: development, reliability and validity. Br J Psychiatry 1996;169:276-281.
37. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry* 2000;31:73-86.
57. Morin CM, Bastien C, Guay B et al. Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry* 2004;161:332-342.
66. Voshaar RC, Gorgels WJ, Mol AJ et al. Tapering off long-term benzodiazepine use with or without group cognitive-behavioural therapy: three-condition, randomised controlled trial. *Br J Psychiatry* 2003;182:498-504.
102. Baillargeon L, Landreville P, Verreault R et al. Discontinuation of benzodiazepines among older insomniac adults treated with cognitive-behavioural therapy combined with gradual tapering: a randomized trial. *CMAJ* 2003;169:1015-1020.PMC236226
103. Garland SN, Carlson LE, Stephens AJ et al. Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. *J Clin Oncol* 2014;32:449-457