1. INTRODUCTION

This is a resubmission of application 1 R01 MH091053-01 entitled "Sequenced Therapies for Comorbid and Primary Insomnias" which received a priority score of 27 (20th percentile). This section addresses the most critical issues raised in the summary statement; additional responses are provided in the application.

1. Despite some overlap with our previous work (e.g., comparison of CBT and medication), this amended proposal offers several novel features about the specific content and sequencing of therapies. Rather than using the full CBT package during first stage therapy, we will use only the behavioral therapy (BT) component along with sleep hygiene education. This abbreviated approach is likely to be more cost-effective so as to optimize its transferability to clinical practice. Cognitive therapy (CT) will be introduced only during second stage therapy because this component may not be essential for a substantial proportion of patients with insomnia and it is also more time consuming than BT. However, because CT has unique features in targeting some perpetuating mechanisms (e.g., worries) shared by insomnia and some psychiatric disorders (e.g., anxiety and depression), introducing CT separately from BT will provide an opportunity to evaluate its specific contribution to outcomes among individuals with and without psychiatric comorbidity.

2. This revised design will also address another concern of the committee in making the switch within the psychological treatment modality (from BT to CT) more equivalent conceptually to the switch within the pharmacological modality (from zolpidem to trazodone); indeed, both second therapies (CT and trazodone) of these sequences have mechanisms of action presumed to address sleep and mood symptoms.

3. The rationale for selecting zolpidem and trazodone as first- and second-stage medication therapies was based on several considerations. One priority was to choose medications that are widely used in practice so that the results would be generalizable to the practice setting. A second consideration was to choose medications with evidence of efficacy for the intended population (i.e., patients with Primary and Comorbid Insomnias). Further, we sought to use a medication in the second stage with a different mechanism of action relative to that used in the first stage because of the likelihood that some individuals will respond differentially as a function of drug mechanism. Additional justification for selecting zolpidem 10 mg as first stage therapy and trazodone 50-150 mg for second stage therapy is provided in the text (see significance and approach).

4. The issues concerning psychiatric comorbidity (recruitment, assessment, rationale of hypothesis) have been clarified in the approach section. We will recruit about 60% of patients with psychiatric comorbidity, with an equivalent mix of patients with mood (e.g., MDD, Dysthymia) and anxiety disorders (e.g., GAD, PTSD). The SCID will be used to assess comorbid psychiatric disorders and the BDI/BAI scores will no longer be used as exclusionary criteria. The rationale for predicting poorer treatment response in Comorbid Insomnia (CMI) relative to Primary Insomnia (PI) is based partly on our previous findings[1] that CMI patients had lower remission rates to CBT relative to PI on categorical measures similar to the primary endpoint used in the present study (i.e., Insomnia Severity Index; ISI). Also, recent data from clinical trials of BzRAs and eszopiclone suggest larger ISI-based treatment effect sizes (0.87) for PI patients relative to effect sizes (0.46-0.48) in patients with comorbid GAD and MDD. Hence, we expect the treatment response of CMI patients as measured by the ISI will be more blunted to both first stage therapies (BT and BzRA medication) than that shown by PI patients; however, second-stage therapy with CT and trazodone is expected to have an added value for CMI patients because these therapies address both sleep and mood symptoms .

5. Attrition rates during first-stage treatment are expected to be around 10% and 20% for behavioral and medication therapies, respectively, with similar rates during second-stage therapy. An additional 10% attrition is expected at 12-month follow-up. We believe these figures to be realistic because they are based on actual data from previous studies conducted at Laval and Duke in which patients received CBT, with or without medication, and no placebo condition was used. For instance, in a recent trial of CBT and medication[2], pooled attrition rates across conditions averaged 8% after first stage treatment (6 weeks), 12% after extended treatment (6 months), and 22% at 12-month follow up. Ongoing contacts with patients after treatment completion, combined with financial incentives to complete assessment forms, are likely to minimize attrition. Should attrition be higher than expected, we are prepared to enroll an additional 10 to 20 patients at each site.

6. Additional issues. The exploratory aim about predictors of treatment response has been deleted as it was not providing critical new information relative to the added participants' burden. Issues related to linear mixed models, missing data, and power have been addressed directly in the revised statistical section.

We believe these changes (highlighted in the text via Georgia font) have strengthened our application and are confident the sequential treatment study we are proposing will markedly advance our knowledge and provide much needed guidance about how best to manage patients with chronic comorbid and primary insomnias.

2. SPECIFIC AIMS

Chronic insomnia is widely prevalent and associated with enhanced health care costs, impaired functioning, and increased risks for psychiatric illnesses such as Major Depression. Cognitive-behavioral therapies (CBTs) and benzodiazepine receptor agonists (BzRAs) are the best evidence-based insomnia treatments. CBTs are well tolerated, preferred by many patients, and have sustained efficacy up to two years following initial treatment; however, they may be time-consuming and providers with CBT expertise are relatively scarce. BzRAs typically produce immediate sleep improvements, are supported by substantial acute treatment efficacy data, are widely used and easy to administer, and are generally well-tolerated; however, there is more limited evidence for sustained efficacy and concerns persist regarding adverse effects. Unfortunately, few studies have compared the acute and longer-term efficacy of CBT and BzRA insomnia therapies and these are limited by small sample sizes, highly selected subjects, fixed-dose/fixed-agent pharmacotherapies that do not represent standard clinical practice, and relatively short follow-up intervals. Moreover, research designed to determine the specific treatment needs of insomnia patients with psychiatric comorbidities or what to do when initial treatment of such patients fails is generally lacking. Finally, most studies have lacked clinically relevant indicators of remission.

The primary objective of this study is to compare short- and long-term outcomes of CBT and BzRA therapies, the two best supported treatment modalities for chronic insomnia. Innovative features that will give this study unprecedented generalizability and clinical relevance include: a sample comprised of a sizable cohort with insomnia occurring comorbid to several psychiatric conditions (CMI); using insomnia remission as the primary outcome; and a sequenced treatment algorithm for moving initial non-remitters into the second-stage therapies. The 320 patients enrolled will be randomly assigned to first-stage treatment with zolpidem (the most widely used BzRA) or behavioral insomnia therapy (BT), an easy to administer intervention with strong evidence of sustained efficacy. Centrally trained therapists will deliver manualized treatments with ongoing review of treatment integrity. Insomnia status will be assessed at the end of 6 weeks of therapy. Treatment remitters will be followed for the next 12 months on maintenance therapy. Non-remitters will be re-randomized to a second-stage treatment involving pharmacotherapy (zolpidem or trazodone) or psychological therapy (BT or cognitive therapy-CT). All participants will be re-evaluated after 6-weeks of the second-stage therapy, and at 3-, 6-, 9-, and 12-month follow-ups. Insomnia remission, defined as a score of less than 8 on the Insomnia Severity Index, will serve as the primary outcome. Secondary outcomes will include sleep variables from diary and PSG measures; ratings of sleep quality and daytime function; adverse events; and treatment acceptability.

Specific Aims/Hypotheses

Aim 1: To compare BT and zolpidem as first-stage therapies for chronic insomnia and examine the moderating effect of psychiatric comorbidity on outcomes.

- **Hypothesis 1a:** The proportion of patients achieving remission with first-stage therapy and sustain remission through follow-up will be higher among those receiving BT than among those receiving zolpidem.
- **Hypothesis 1b:** A lower proportion of the CMI patients will achieve remission with first stage therapies than will those with primary insomnia (PI).
- **Hypothesis 1c:** Secondary outcome measures will show greater improvements through treatment and follow-up for those receiving BT than among those receiving zolpidem.

Aim 2: To evaluate specific first-stage→second stage treatment sequences and examine the moderating effect of psychiatric comorbidity on outcomes. To address this Aim, we will conduct pair-wise comparisons among two types of sequences: 1) switching modalities (BT→zolpidem or zolpidem→BT); 2) staying within a modality (BT→CT or zolpidem→trazodone).

- **Hypothesis 2a:** The insomnia remission rate at the end of second-stage treatment (for all conditions combined) will be 20% higher than with first-stage treatment (increment from 40% to 60%).
- **Hypothesis 2b:** Of all PI patients who enter second-stage treatment, a greater proportion that switches modalities (i.e., BT→zolpidem or zolpidem→BT) will achieve remission and sustain it through follow-up than among patients who stay within a treatment modality.
- **Hypothesis 2c:** Among CMI patients who enter second-stage treatment, there will be a higher remission

rate among those receiving treatments that address sleep and mood symptoms (CT and trazodone) than among patients receiving treatments designed mainly to improve sleep (BT and zolpidem). This added therapeutic benefit will be higher for CMI than for PI patients.

- **Hypothesis 2d:** Secondary outcomes will show response patterns consistent with Hypotheses 2a-c.

3. RESEARCH STRATEGY

(a) Significance: Insomnia is characterized by difficulties initiating, sustaining, or obtaining qualitatively satisfying sleep that occur despite adequate sleep opportunities/circumstances and result in notable waking deficits[3, 4]. Over 33% of adults experience insomnia at least intermittently, whereas 10% to 15% suffer chronic, unrelenting sleep difficulties[5-9]. Although its significance is often minimized[10, 11], persistent insomnia may lead to daytime fatigue, decreased mood, impairment in social/vocational functioning and reduced quality of life[12-15]. Insomnia also increases the risks for serious medical disorders, traffic and work-site accidents, alcohol/drug abuse, and major psychiatric illnesses[6, 16-22]. When insomnia occurs co-morbid to a psychiatric illness such as major depression, it complicates disease management and often remains as a residual symptom that enhances risk for both suicide and relapse[23-26]. Moreover, insomnia contributes to increased health care utilization and costs. Indeed, insomnia sufferers spend well over $285 million per year for prescription sleeping pills whereas the annual direct, treatment-related costs of insomnia in the U.S. may exceed $90 billion[27, 28]. More than 90% of insomnia-related costs are attributable to work absences and reduced productivity[29]. In view of these considerations, ascertaining the most effective and enduring treatments for the many who suffer chronic insomnia should be a priority for our health care system and for our nation.

WHAT INSOMNIA TREATMENT OPTIONS ARE CURRENTLY AVAILABLE? Several pharmacological treatment options are available for insomnia management. The most popular agents are the benzodiazepine receptor agonists (BzRAs) which bind to the $GABA_A$ receptor complex [28, 30]. In so doing, these agents enhance the sleep promoting effects of homeostatic sleep-drive and decrease activity in arousal systems (acetylcholine, histamine, orexin/hypocretin, serotonin, etc.)[31]. BZRAs include several benzodiazepines (e.g., temazepam, triazolam, etc.) and newer non-benzodiazepine agents (e.g., zolpidem, eszopiclone,). Additionally, the melatonin agonist, ramelteon, is FDA-approved for insomnia therapy, though its sleep improving mechanisms are unknown. Finally, off-label use of antihistamines and sedating anti-depressants such as trazodone (TRZ)[28] and tricyclic antidepressants (e.g., amitriptyline, doxepin)[28] has been popular for insomnia management. These agents enhance sleep by diminishing arousal through blocking the effects of wake-promoting systems[31].

Complementing these pharmacotherapies are a variety of psychological therapies. These treatments address one or more of the psychological/behavioral mechanisms thought to perpetuate insomnia such as maladaptive sleep habits, dysfunctional beliefs about sleep, excessive cognitive or physiological arousal, and poor sleep hygiene practices [32-35]. Included among these approaches are various stand-alone strategies such as stimulus control, sleep restriction, relaxation training, paradoxical intention, sleep hygiene education, and cognitive therapy. In addition, multi-component, cognitive-behavioral insomnia therapies (CBTs) that combine several of these therapies to optimize outcomes have become the most frequently used approaches.

HOW EFFECTIVE ARE THE AVAILABLE INSOMNIA THERAPIES? Of the various prescription medications used for insomnia treatment, FDA-approved BzRAs have the most efficacy and safety data and consequently have come to be regarded as first-line insomnia therapies. A meta analysis[36] of 22 placebo-controlled trials involving traditional BzRAs and zolpidem with primary insomnia (PI) patients showed these agents produce reliable short-term (median treatment duration = 7 days; range = 4-35 days) improvements of sleep-onset latency (mean effect size = 0.56), number of awakenings (effect size = 0.65), total sleep time (effect size = 0.71), and sleep quality (effect size = 0.62). Furthermore, a few recently published trials[37, 38] have shown the newer BzRAs such as zolpidem have continued efficacy and safety for periods of 3-12 months of nightly use. Whereas studies of BzRAs with insomnia occurring comorbid to a mental disorder (CMI) have been limited, there are some data showing that combining a BzRA with antidepressant medications (SSRIs) is significantly more efficacious than SSRIs alone for treating both insomnia and depression in patients with major depressive disorder[39-42]. In contrast, trazodone and most sedating tricyclic antidepressants lack FDA approval for insomnia management since data supporting their efficacy with insomnia patients is extremely limited. Yet, trazodone has been used widely "off-label" for insomnia treatment[28] and there are some data supporting the efficacy of this agent for treating insomnia occurring with ongoing mood disorders such as major depression[43-47].

Like the BzRAs the psychological/behavioral insomnia therapies are well supported and can be considered first-line treatments. Several meta-analyses[48-51] that considered over 50 published trials with PI sufferers show such treatments produce moderate to large improvements in sleep onset latency (effect sizes =

.87-.88), total sleep time (effect sizes = 0.42-0.49), number of awakenings (effect sizes = 0.53-0.63), duration of awakenings (effect size = 0.65), and sleep quality ratings (effect size = 0.94). Overall, between 70%-80% of treated PI patients benefit from treatment, with the best outcomes resulting from multi-faceted therapies such as CBTs [33, 51-53]. Applications of these therapies to CMI patients have been more limited, but the available data suggest these treatments produce sleep improvements among insomnia patients with chronic peripheral pain syndromes[54], breast cancer[55], fibromyalgia[56], mixed medical disorders[57], alcoholism[58], and depression [59, 60]. Previous findings also suggest that these therapies lead to improvements in mood status, enhanced likelihood of depression remission, and reductions in other disease-specific symptoms among CMI patients[55, 56, 59, 61, 62]. Thus, the psychological/behavioral therapies hold promise for CMI patients as well as for those with PI.

WHAT SHOULD BE OUR FIRST STAGE INSOMNIA THERAPY AND WHAT SHOULD WE DO WHEN THAT FAILS? Deciding whether to use pharmacological or psychological/behavioral insomnia therapy in general or with specific patients is difficult, since both forms of treatment have their limitations. Medications usually produce rapid improvements, are widely available, and generally well tolerated, but adverse effects including residual daytime sedation, reduced motor coordination, cognitive impairment, tolerance, and rebound effects may complicate their use[63-65, 66-68]. Furthermore, there are no data documenting enduring benefits of these agents after their use is discontinued. In contrast, the psychological/behavioral insomnia therapies have minimal side effects, are preferred by many patients, and typically result in enduring sleep improvements long after termination of acute treatment[48, 51]. However, these therapies require more extensive provider contact and have a slower rate of therapeutic action than do medications[69, 70]. In addition, they are less widely available than BzRAs despite recent efforts to provide their wider dissemination through abbreviated therapy protocols[71, 72], self-help interventions[73], and the training of non-traditional providers[74].

Whereas the relative value of BzRA and psychological/behavioral therapies largely depends upon their comparative efficacies and safeties, there have been few head-to-head comparisons of these treatments. One recent trial[75], which compared CBT with the BzRA, zopiclone, over a 6-week acute treatment phase and subsequent six-month follow-up, showed CBT produced significantly better short- and longer-term improvements on objective (PSG) indices but not on subjective (sleep diary) measures. A few other studies[69, 76, 77] that compared a single-agent BzRA therapy, CBT, and combined BzRA/CBT therapy showed little difference in short-term outcomes, but superior longer-term outcomes with CBT compared to BzRA and combined treatment. In contrast, a recently published trial showed a sequential treatment strategy that commenced with 6 weeks of combined CBT/BzRA therapy followed by an extended six months of CBT alone proved superior to continued long-term combined therapy or CBT provided in the absence of any medication [2]. However, these studies are limited by their small sample sizes, use of fixed-dose/fixed-agent pharmacotherapy strategies that do not represent standard clinical practice, and/or their exclusive focus on PI patients. Hence, these findings provide very limited guidance for deciding upon the optimal first-stage insomnia therapy in general and specifically for the prominent and challenging subgroup of CMI patients with psychiatric illnesses.

Further complicating matters are a number of additional oversights in the insomnia treatment literature that limit its usefulness for guiding clinical practice. First, most previous treatment studies have focused on changes in individual quantitative sleep measures (e.g. sleep onset latency, total sleep time) to gauge treatment outcomes. These indices are important, but they miss other relevant symptoms such as daytime fatigue, cognitive efficiency, and overall sleep satisfaction which patients regard as particularly important and clinicians use to assess global improvement[78-81]. Moreover, few studies have assessed treatments using validated measures of insomnia remission, the outcome most relevant to clinical practice. Secondly, it remains unclear how well CMI patients respond to the standard doses/protocols of insomnia therapies established for PI patients. Emerging evidence[82] suggests CMI patients demonstrate greater adherence difficulties to CBT than do PI patients, and our own data (see preliminary studies) indicate CMI patients show a less robust CBT response than do PI sufferers when global insomnia syndrome measures are considered. Likewise, recent studies[83] using the Insomnia Severity Index[84] to assess the efficacy of the BzRA, eszopiclone, show large treatment effect sizes = 0.87 for PI patients but smaller effect sizes = 0.46 and 0.48 in patients with comorbid generalized anxiety disorders and major depression respectively. CMI patients, thus, may have a more blunted response to first-stage insomnia therapy than do PI patients regardless of the specific modality they receive. Finally, extant data shows a large proportion of patients fail to remit with first-stage therapy and are, thus, left with residual insomnia symptoms.[51] In such situations, switching from one therapy to another, on a trial-error basis, is common clinical practice. Yet, no studies have addressed such important questions as: (1) *Which second-stage treatment offers the best hope for insomnia remission, once a reasonable course of a psychological or medication first-stage therapy fails to achieve this endpoint? and (2) Do the optimal first-*

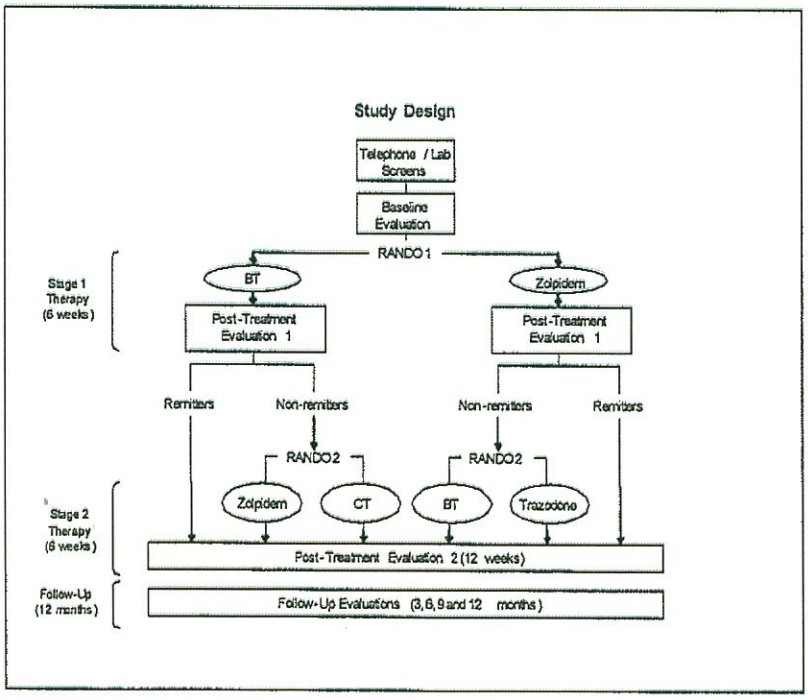
stage-to-second-stage treatment sequences differ for those with CMI and PI?

When selecting first stage therapies to test, we chose two distinctive treatment modalities that are well supported, relatively easy to administer, and frequently used. One is the medication, zolpidem, which has well established efficacy and is now the most often prescribed BzRA for insomnia[43]. Our alternate first line therapy will be a behavioral therapy (BT) comprised of stimulus control, sleep restriction, and sleep hygiene education. Although multi-component CBT may represent the psychological treatment of choice, we have chosen to employ only its core behavioral elements so as to make this therapy easy to deliver and ultimately more transferable to clinical settings. BT and Zolpidem will also serve as second-stage therapies so that we can assess effects of switching from one type of sleep-focused therapy to another (e.g., BzRA→BT) We chose trazodone as an alternate second-stage pharmacotherapy since this medication has enjoyed wide off-label use as a sleep aid over the past several decades, a different mechanism of action than BzRAs, and proven efficacious among CMI patients with mood disorders[43, 46, 47]. Finally we chose to test the Cognitive Therapy (CT) component of CBT as an independent second-stage treatment. CT seems reasonable to choose as a second stage therapy since it is time consuming to deliver and not essential for all insomnia patients. Yet, CT is designed to target critical cognitive perpetuating mechanisms for insomnia (worries, self-monitoring, negative automatic thoughts), some of which may be shared with other psychiatric disorders (e.g., anxiety and depression). These cognitive factors are not specifically addressed by BT. Thus, CT's impact could be broader and improve mood and sleep, a very desirable outcome among patients with comorbid psychiatric disorders.

(b) Innovation: The proposed project entails a dual-site, open-label trial examining sequential treatment with well-supported and commonly used therapies to asses their relative efficacy and safety. This project has the following innovative features designed to advance understanding of the treatment needs of insomnia sufferers, particularly those with treatment-resistant psychiatric illnesses: (1) Enrollment of participants with broadly-defined chronic insomnia disorder, with and without psychiatric comorbidity; (2) use of the clinically-relevant primary outcome, insomnia remission, rather than the traditional, less relevant quantitative parameters (e.g., sleep time, sleep onset latency); (3) use of a sequential treatment design that tests various first-stage-to-second-stage treatment sequences; (4) flexible medication dosing, rather than a fixed-agent/fixed dose design; and (5) plans to systematically collect AE data for both psychological and medication therapies so that the relative safety of the two approaches can be examined. This project should provide new and relevant information that contributes to the development of clinical guidelines for CMI and PI management, guidelines which are critically lacking[85].

(c) Approach:

c.1 Study Design and Rationale. Adults with chronic insomnia (n = 320) will be randomly assigned to zolpidem therapy (MED; n = 160) or behavioral therapy (BT; n = 160), stratified by gender, age (< 55 years vs. ≥ 55 years), and insomnia subtype (primary-PI vs. comorbid-CMI). We expect roughly 50% of our sample will be ≥ 55 years old, about 60% will be women, and we will recruit 60% with insomnia comorbid to a mental disorder. We will monitor other variables (e.g., prior usage of hypnotic medications) that might be related to treatment response and, if necessary, control for these in statistical analyses. After completing the initial 6-week treatment phase, treatment remitters will remain on maintenance therapy. Non-remitters will be encouraged to accept randomization to a second-stage alternate therapy provided over the next 6 weeks. Participants treated with BT initially will receive another psychological treatment, CT, or a medication therapy (zolpidem). Those treated with medication (zolpidem) initially will be switched to BT or to a different medication (trazodone). Measurements will be taken at baseline, at the end of first- and second-stage therapies (i.e., weeks 6 and 12), and at follow-ups conducted 3, 6, 9, and 12 months after the week 12



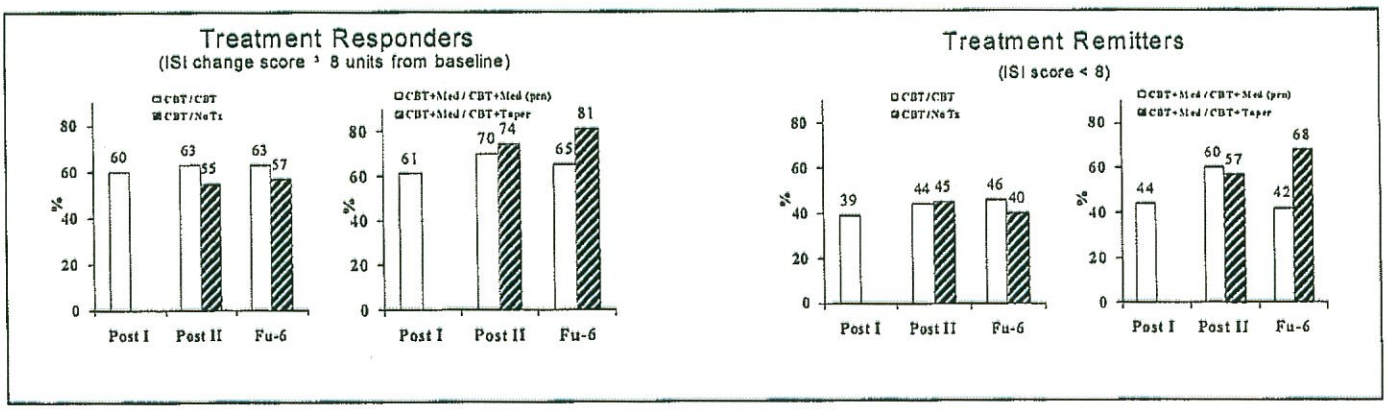
assessment.

This study design derives from our primary aims: (1) to compare outcomes of BT and zolpidem when provided as first-stage therapies for insomnia patients with/without psychiatric comorbidity and (2) to assess the *value-added* of switching strategies for those not achieving remission with first-stage therapy. The BzRA, zolpidem is included because it is readily available and the most widely used pharmacotherapy for insomnia. BT was chosen for comparison because it is an effective, pragmatic, and safe treatment option that is preferred by many patients. Evidence suggests both BZRAs and BT produce a treatment response in roughly 60%-70% of patients, although only about 40% of all patients achieve remission. The second-stage treatments will show whether added efforts involving changing therapy within a broad treatment class (psychological or medication), or switching to an alternate mode of therapy will bring more patients into remission.

Several alternative conditions were considered when planning this study. For instance, although CBT is becoming the standard approach to treating insomnia, we decided to introduce its two main therapeutic components (BT and CT) in a sequential fashion rather than as a treatment package. First, there is much stronger evidence supporting BT than CT; in addition, BT is easier to implement than CT (by non-specialists), thus enhancing its transferability to clinical practice. We also considered using a combined treatment involving concurrent use of medication and CBT but decided against this option because it is rarely available as a first-stage therapy and because the evidence suggest that combined CBT/MED therapy is not necessarily optimal, when long-term outcomes are considered. Our study design provides a unique opportunity to test the impact of sequential rather than concurrent therapies. We also considered including a placebo-control condition but decided not to do so because our research questions are not about documenting treatment efficacy relative to placebo; such data are already available. Rather, our main questions concern the comparative efficacy of first-stage psychological and pharmacological therapies and their optimal sequencing as second-stage therapies for CMI and PI. In the end, we believe the design chosen is the most appropriate to answer our specific research questions, while offering the best compromise in terms of feasibility, cost, and statistical power.

c.2 Preliminary Studies. The preliminary studies (a) show the PIs' experience and leadership in conducting RCTs of insomnia therapies, (b) provide rationale for the therapies chosen and study hypotheses and, (c) support the feasibility of the project proposed (See Appendix 1 for overall collaborative plan).

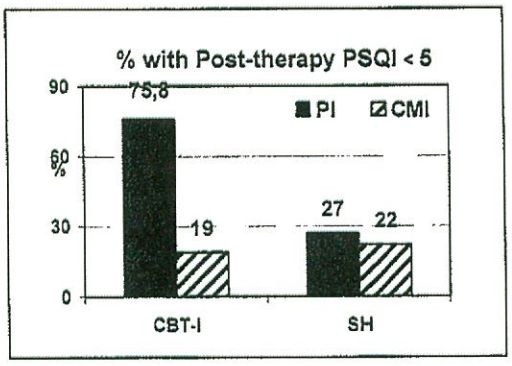
CBT and Medication for Persistent Insomnia: Short-Term and Maintenance Treatment Effects.[2] Dr. Morin's group conducted this study to evaluate the short-term effects of CBT, alone and combined with medication, and to compare effects of varied treatment sequencing strategies on long-term outcomes. A total of 160 chronic insomnia patients (61% women; mean age of 50.3 yrs) were randomized to CBT (n = 80) or CBT plus nightly 10 mg zolpidem (n = 80) for an initial 6-week treatment. After completing this treatment, they were randomized again for an extended 6-month treatment. Patients initially treated with CBT alone continued with extended individualized CBT or received no additional treatment; those who received combined treatment initially continued with an extended treatment consisting of CBT plus intermittent medication (10 pills per month) or CBT alone. Of the 160 patients enrolled, 148 completed acute treatment, 141 completed extended treatment, and 127 patients were available at 6-month and 125 at 12-month FUs (overall attrition rate of 22% over a 1-year period). Outcomes were examined in terms of treatment response (change on the Insomnia Severity Index (ISI) > 7) and remission (ISI value < 8). Although the proportion of treatment responders was comparable with CBT alone (60%) and CBT plus medication (61%) at the end of acute treatment, different trajectories of change emerged over the following 6 months depending on whether therapy was provided. More patients responded with maintenance CBT than without (63% vs. 55%). Also, patients treated with combined



therapy initially did slightly better during maintenance therapy when medication was stopped compared to intermittent usage (74% vs. 70% responders), and this trend became significant at the 6-month follow-up (81% vs. 65%). A similar pattern emerged regarding remission. Remission rates were 39% (CBT alone) and 44% (CBT + medication) after acute therapy, and there was no significant difference after extended therapy between CBT and no additional treatment or between CBT alone and CBT plus intermittent medication. At the 6-month follow up, however, remission rates were significantly higher among those who had received maintenance CBT than among those who did not (46% vs. 40%) and among those who discontinued medication versus those who continued with intermittent medication (68% vs. 42%). These findings, while preliminary, have implications for the current proposal. First, CBT + medication may not provide a strong advantage over CBT alone, at least on acute outcome. Second, the addition of a second-stage alternate psychological therapy may enhance long-term remission rates. Thirdly, when combined therapy is used as first-stage therapy, long-term remission rates may be enhanced by tapering medication while patients are still receiving CBT. Although informative, these conclusions remain tentative because the findings were based on a limited sample obtained at only one site and only patients with primary insomnia were enrolled. In addition, the study made no comparison between CBT alone and medication alone. Moreover, the randomization to second-stage therapy did not consider initial treatment response, a factor that should guide second-stage therapy.

Instability of sleep and bedtime arousal in CMI and PI patients[86]. This study conducted by Dr. Edinger's group, examined patterns of sleep disturbance and bedtime arousal in individuals with PI and CMI related to a mental disorder. The study included 187 insomnia sufferers (126 women, M_{Age} = 47 years) assigned either PI (n = 126) or CMI (n = 61) diagnoses by 6 sleep specialists at one or the other of two collaborating medical centers. Results showed CMI patients displayed significantly longer SOL, on average, and significantly more instability across nights in their TST (i.e., larger changes) than did PI patients. CMI patients exhibited higher levels of somatic, cognitive and emotional arousal as well as more instability on nightly ratings of emotional arousal. Correlations revealed a significant relationship between pre-sleep arousal and SOL in the PI group (r values from 0.26 to 0.34), whereas corresponding correlations between all sleep and bedtime arousal measures were non significant in the CMI group (r values < 0.14). Despite greater levels of arousal and longer SOLs in the CMI group, they showed less correspondence between sleep and arousal than did the PI group. The findings imply these two groups have different perpetuating mechanisms and treatment targets/needs.

Psychiatric comorbidity as a moderator of CBT response[1]. Dr. Edinger's group also conducted this study to determine if PI and CMI patients derive comparable benefits from CBT. Participants (70 men, 11 women; M_{Age} = 54.2 ±13.8 yrs.) met criteria for PI (n = 40) or CMI (n = 41). Most of the CMI patients met criteria for a depressive disorder (MDD or dysthymia; n = 16) or combat-related Posttraumatic Stress Disorder (n = 18). Patients were randomly assigned to either CBT or a sleep hygiene control therapy (SH) entailing lifestyle (e.g., limit caffeine) and environmental manipulations (e.g., keep bedroom dark) to enhance sleep. Each treatment consisted of 4 biweekly, 30- to 60-minute individual sessions with a study therapist.



Comparisons of these groups using traditional quantitative sleep parameters (e.g., TST, SOL) suggested no consistent differences in their relative CBT responsiveness. However when more global measures of the overall insomnia syndrome were considered, the PI group was more responsive to CBT than the CMI group. For example, on the Insomnia Symptom Questionnaire, an instrument designed to assess changes in both daytime and nighttime symptoms, CBT-treated PI patients displayed a much larger treatment effect size (.87) than did CBT-treated CMI patients (.34). Moreover, 75.8% of the CBT-treated PI patients achieved normal scores on the Pittsburgh Sleep Quality Index by the end of treatment, compared to only 19% of the CBT-treated CMI patients (see figure). These two instruments most closely approximate the global insomnia disorder assessment provided by the Insomnia Severity Index, which will serve as the primary outcome for the project proposed. Thus, we believe these data suggest BT-treated CMI patients will have a lower ISI measured remission rate following first-stage treatment than will BT-treated PI patients.

c.3 Subjects

Selection Criteria. We will recruit adults (aged 21 and older) with chronic insomnia from the community and from outpatient medical and mental health clinics. Inclusion criteria will be broad to obtain results widely generalizable to the insomnia patient population commonly seen in practice. The inclusion criteria are: (a) a

complaint of persistent (i.e., ≥ 1 month) difficulties initiating or maintaining sleep despite adequate opportunity for sleep; (b) a sleep onset latency or wake time after sleep onset > 30 minutes 3 or more nights per week during two weeks sleep diary monitoring; (c) an Insomnia Severity Index (ISI) score > 10 indicating at least "mild" insomnia; and (d) a score ≥ 2 on either the interference or distress item of the screening ISI, indicating the insomnia causes significant distress or impairment in social, occupational, or other areas of functioning. These criteria represent those provided in the DSM-IV-TR[87], Research Diagnostic Criteria[3] and the International Classification of Sleep Disorders[4], and will ensure a sample with clinically relevant insomnia.

Exclusion criteria will be minimal to retain a broadly representative sample that includes patients with primary and insomnia comorbid to a psychiatric disorder. Likewise, individuals with a comorbid medical condition will be excluded only if the medical condition is life-threatening or would contra-indicate using study medications. Exclusion criteria are (a) an untreated psychiatric disorder (e.g., major depression) as these conditions have specific treatments and it would be inappropriate not to offer those treatments; (b) a lifetime diagnosis of any psychotic or bipolar disorder as sleep restriction and medications for insomnia may precipitate mania and hallucinations; (c) an imminent risk for suicide; (d) alcohol or drug abuse within the past year, since BzRAs are cross-tolerant with alcohol; (e) terminal or progressive physical illness (e.g., cancer, COPD), or neurological degenerative disease (e.g., dementia); (f) current use of medications known to cause insomnia (e.g., steroids); (g) sleep apnea (apnea/hypopnea index > 15), restless legs syndrome, periodic limb movement during sleep (PLMS with arousal > 15 per hour), or a circadian rhythm sleep disorder (e.g., advanced sleep phase syndrome); (h) habitual bedtimes later than 2:00 AM or rising times later than 10:00 AM; (i) consuming > 2 alcoholic beverages per day on a regular basis.

Individuals using sleep-aids (prescribed or over-the-counter) will be included if they are willing and able to discontinue medications at least 2 weeks before baseline assessment. Participants using alcohol as a sleep aid or alcohol after 7:00pm on a regular basis will be required to discontinue this practice at least two weeks prior to baseline assessment. Individuals using psychotropic medications (e.g., anxiolytics, antidepressants) will not be automatically excluded from the study. Those on stable dosages (for at least three months) of SSRI or SNRI medications and who show at least partial remission (via SCID) from their mood or anxiety disorder will be accepted in the study if they meet the selection criteria above. Patients using TCAs, MAOIs, or atypical antidepressants will be excluded even if in remission as the effects of these medications on sleep might confound interpretation of the findings. We will impose similar standards for those with MDD, dysthymia, panic disorder, phobia, and GAD. We realize that some decisions about enrollment may not always be easy to make, but we will rely on all available data and a consensus approach to guide our clinical decision making process.

Recruitment/Participant Flow. Participants will be recruited at two sites (National Jewish Health and Laval Universities), each of which has an active insomnia research program with proven infrastructures for clinical trials. We will recruit participants through media advertisements, flyers distributed in outpatient clinics, and letters to primary care physicians and mental-health clinicians. We have ongoing referrals from these sources at each study site, including many with difficult forms of insomnia comorbid with psychiatric conditions. We recognize that CMI patients are relatively more prevalent than PI sufferers, and our study aims are designed to determine the optimal treatment(s) for such individuals. We will use a targeted recruitment approach so that roughly 60% (n = 192) of the 320 patients enrolled will have CMI. Given our usual mix of clinic and research referrals, we are confident the CMI patients enrolled will comprise a mixture of anxiety disorders (GAD, panic, phobia, PTSD) as well as mood disorders (e.g. dysthymia) other than major depression so our study results should add to and compliment ongoing NIMH funded trials focused exclusively on CMI in MDD. Based on our previous trials, we expect 400-500 individuals to inquire about the study at each site during the 48 months of enrollment. Approximately 40%-50% should meet study criteria so 3-4 participants are enrolled monthly at each site. We expect that attrition will be limited since study participants will be provided free ongoing treatment and financial incentives. Recent experiences with trials involving behavioral and pharmacological insomnia therapies at both sites have shown attrition rates in the 10% to 20% range. Should attrition be higher than expected, we are prepared to enroll 10-20 additional subjects per site in this trial to maintain adequate statistical power.

c.4 Sleep-Wake Monitoring

Polysomnography. Study participants will undergo standard nocturnal polysomnographic (PSG) monitoring for screening and outcome assessment. The initial PSG will serve to detect sleep disorders that would lead to exclusion (see selection criteria, c.3) and to provide an initial baseline night for those enrolled. Patients who meet criteria will complete additional PSG recordings at various times to assess outcomes (see Table C.5). PSG monitoring will be conducted in the sleep laboratories according to standard procedures with

regard to montage and sampling rate (256 Hz), and bedtimes and rising times. Patients randomized to medication conditions will take their study medication (zolpidem or trazodone) at the time of sleep studies. Participants will undergo PSG on their usual dosages of allowed psychotropics (e.g., SSRI) and other medications (e.g., antihypertensive agents) since these medicated individuals will have active insomnia despite using medications. PSG recordings will be scored, blind to treatment assignment, in 30-second epochs using standard scoring criteria[88] for sleep staging and characterization of sleep-associated events (e.g., apneas). The initial screening/baseline PSG will be scored at the site where it is recorded to ensure a timely decision regarding study inclusion. All remaining PSG records will be scored centrally at the National Jewish Health site by trained technologists under the supervision of Dr. Krystal, an experienced, board-certified polysomnographer.

IVRS Sleep Diary System. Subjective estimates of sleep and wake times will be obtained daily using an interactive telephone voice response system (IVRS). Participants will phone the IVRS system each morning and report the following information about their previous night's sleep: bedtime, sleep onset latency, number and length of nocturnal awakenings, time of final waking, rising time, ratings of sleep *quality* and *restedness* upon arising. Additional questions will query caffeine, alcohol, and sleep medication use. The IVRS program will automatically record a time and date stamp to verify when the data were entered. IVRS sleep diaries will be obtained for 2-weeks at baseline and at each subsequent assessment period.

c.5 Measures

Screening Instruments. Two structured interviews will be used. The *Duke Structured Interview for Sleep Disorders* (DSISD; Appendix II)[89], is an instrument developed by Dr. Edinger and colleagues to assist in ascertaining DSM-IV-TR[87] and International Classification of Sleep Disorders (ICSD-2)[4, 90, 91] sleep disorder diagnoses. This instrument has acceptable reliability and discriminant validity[1]. In addition, the *Structured Clinical Interview for DSM-IV* Axis I Disorders (SCID)[92] will be used to classify enrollees as having primary or comorbid insomnia and to identify study candidates with disorders (e.g., Bipolar Disorder) leading to exclusion. In addition to widespread use in clinical research, the SCID is supported by extensive reliability and validity data. All interviews will be audio taped and reliability checks will be conducted on 15% of them. We will administer the *Folstein Mini-Mental Status Exam* (MMSE)[93] to exclude those with cognitive deficits (MMSE score $\leq$ 27) informed consent will be obtained before any study related procedures are performed.

Outcome Measures. The primary outcome metric will be the proportion of individuals achieving remission by producing scores $\leq$ 7 the Insomnia Severity Index (ISI) [32]. The ISI is a 7-item self-report questionnaire that provides a global measure of perceived insomnia severity based on several indicators (e.g., difficulty falling or staying asleep, satisfaction with sleep, degree of impairment with daytime functioning). The total score ranges from 0-28: 0-7 (no clinical insomnia), 8-14 (sub threshold insomnia), 15-21 (insomnia of moderate severity), and 22-28 (severe insomnia). The ISI has been validated[84] and has proven sensitive to therapeutic changes in several treatment studies of insomnia[69, 94].

We will track a number of secondary outcomes. Among these are measures of sleep/insomnia status including: sleep onset latency (SOL), wake time after sleep onset (WASO), total sleep time (TST), sleep efficiency (SE) taken from both sleep diaries and PSG. Diary ratings of sleep quality and feeling rested upon arising will also be obtained. Patients will complete the *Pittsburgh Sleep Quality Index (PSQI)*[95] at various time points to reflect their changes in overall sleep quality. The PSQI is widely used in clinical research and has validated cut-off scores to optimize sensitivity and specificity as a measure of insomnia[96, 97] A *clinical global improvement (CGI)*[98] rating will be completed by a blinded rater to provide a measure of insomnia severity and intervention effects. Despite some limitations about reliability and validity[99], the CGI will serve as a useful comparator with other insomnia trials. Finally the blinded rater will interview participants at the conclusion of their study involvement using the DSISD to determine whether they continue to meet RDC for insomnia.

To reflect treatment-related changes in daytime function, participants will complete the *Multidimentional Fatigue Inventory (MFI)*[100], the *SF-36 Health Survey (SF-36)*[101] and the insomnia adaptation of the *Sheehan Disability Scale (SDS-I)*[102]. The well-validated[100] 20-item MFI assesses several dimensions of fatigue (e.g., physical, mental) and has been used in studies of chronic pain[103], cancer [104] and depression [105]. The SF-36 is a quality of life measure that comprises eight scales (e.g., Physical functioning, Bodily Pain, Vitality) and 2 summary measures (Physical Health and Mental Health)[106, 107]. The SDS-I measures impairment in three major areas of functioning: work, social life/leisure activities, and home life/family responsibilities. It has been widely used in clinical trials for anxiety and depressive disorders and, more recently, in insomnia trials[108].

Changes in mood status will be assessed by including such well-validated and widely used measures as the *Beck Depression Inventory-II (BDI-II)*[109], *State-Trait Anxiety Inventory (STAI)*[110] and the *Beck Anxiety*

Inventory (BAI)[111]. These instruments have well-established psychometric properties and have been used extensively in clinical research including studies of insomnia [112].

Adverse events (AE) monitoring will be achieved by using the *Systematic Assessment for Treatment Emergent Events (SAFTEE)* a reliable and valid instrument for assessing AEs related to study treatments.[113, 114] Finally, we will use an amended version of the *Therapy Evaluation Questionnaire* (appendix III) to assess treatment credibility, acceptability and patient satisfaction[115].

c.6 Procedures

Study candidates will undergo a multi-level screening. After an initial telephone screening, they will complete: (a) the DSISD[89], SCID[92], and MMSE; (b) a medical history, physical exam, and may have laboratory tests (e.g., CBC, electrolytes, thyroid function tests, ECG, drug/alcohol screen); (c) a qualifying ISI; (d) 2 weeks of the IVRS sleep diary. Laboratory tests will be ordered at the time of initial medical screening for the study when medical symptoms or history dictate the need for such tests. For example: a patient with a known history of thyroid disease could have a panel ordered if the patient's thyroid levels have not been checked within the past year or if a recent panel conducted elsewhere showed values out of the normal range; a CBC could be ordered if there is a known chronic history of anemia; an ECG could be ordered for a patient with an abnormal cardiac history when a previous ECG cannot be obtained; drug and alcohol screens could be ordered to rule out current substance use if behavioral patterns or history suggest probable ongoing substance abuse problems. These are the main sorts of situations wherein such laboratory tests could be ordered. In general such test will be ordered as needed to protect patient safety and health during the study. When obtained, clinical and laboratory data will be reviewed on an ongoing basis in order to ascertain patients' suitability for the study.

Table C6. Time Course of Assessment and Study Procedures

	Screen	Baseli	Treatment 1		Treatment 2		Follow-up			
MEASURES/TIME	- 4 weeks	-2	WKs 1-	Wk #	Wks 7-	Wk	3	6	9	12
Telephone Screening	X									
Clinical evaluation of Insomnia – DSISD+RDC	X									
Urine Pregnancy Test	X									
SCID/Psychological Screening	X			X		X		X		X
Medical History/Physical Exam	X			X		X		X		X
Polysomnography - # of nights		2		2		2				
Sleep Diary	2	2	X	X	X	X	X	X	X	X
Insomnia Severity Index & Pittsburgh Sleep Quality Index	X	X	ISI	X	ISI	X	X	X	X	X
CGI + RDC assessment			CGI	X	CGI	X	X	X	X	X
Psychological Measures - BDI, STAI, BAI		X		X		X	X	X	X	X
Daytime Functioning – SF-36, MFI, SDS-I, Work and Social Adjustment Scale		X		X		X	X	X	X	X
Adverse Events Assessment – SAFTEE		X		X		X	X	X	X	X
Treatment credibility, preference,		X	Wk 1	X	Wk 7	X		X		X

Study candidates who meet selection criteria will complete PSG to rule other sleep disorders (e.g., apnea and PLMS). In the absence of such disorders during the first PSG night, a second consecutive PSG will be conducted for baseline purposes. Participants will then complete baseline assessment: (a) 2 weeks of nightly IVRS sleep diary monitoring; (b) self-rated questionnaires (c) clinician-administered assessments (ISI, CGI, RDC & SAFTEE adverse events). Participants will then be randomized to BT (n = 160) or MED (n = 160) treatments stratifying by gender, age, and psychiatric comorbidity. The latter classification will consider RDC and SCID criteria to determine whether patients have primary insomnia (PI) or comorbid insomnia (CMI).

During initial treatment with BT or MED, participants' ISI scores obtained at weeks 5 and 6 of treatment will be examined. Those who reach insomnia remission (ISI < 8) will receive no more provider contact but will continue their first-stage therapy independently for the next 6 weeks. Those who do not remit (ISI ≥ 8) will be encouraged to accept second stage therapy. Those who accept a second treatment will be randomized to an alternate insomnia therapy over the ensuing 6 weeks. Non-remitters who decline second-stage therapy will end their study participation at this point. During this second treatment phase, all participants will continue to collect nightly sleep diary data and complete the ISI (weekly) and other outcome questionnaires (at week 12), whether they receive a second therapy or not. Those receiving second-stage therapy will complete two PSG nights at week 12. Subsequently, all participants will enter follow-up wherein they will be contacted on a monthly basis for adverse event monitoring. Most such contacts will be by phone, but in-person visits will occur at months 3, 6, 9 and 12, when participants will be asked to complete additional IVRS sleep diaries (2 weeks), outcome questionnaires, and the SAFTEE. At the 12-month follow-up, a blinded clinician will use the DSISD to determine if participants meet RDC criteria for insomnia disorder (see Table C6 for sequence of procedures).

c.7 Treatments

Psychological Therapy. The first-stage psychological therapy will be Behavioral Therapy (BT), comprised of sleep restriction[116] and stimulus control therapies[117]. These well-established strategies are designed to strengthen homeostatic sleep drive, consolidate sleep via reducing time in bed, establish a regular sleep schedule, and curtail sleep-incompatible behaviors. Sleep hygiene education also will be included in BT to address lifestyle (e.g., caffeine use) and environmental factors (e.g., light, noise) that affect sleep.

The second-stage psychological treatment will consist of Cognitive Therapy (CT). CT is aimed at altering sleep-disruptive and mood-disturbing cognitions that exacerbate the vicious cycle of insomnia. Such cognitions are typically related to thoughts and beliefs about unmet sleep requirements (e.g. "I must have 8 hours of sleep every night") and potential insomnia consequences (e.g., "insomnia is necessarily detrimental to health and productivity"). Perpetuating mechanisms such as excessive self-monitoring and worries are also prime targets for CT. CT will follow standard procedures to identify and alter these sleep-interfering cognitions via recording automatic thoughts, Socratic dialogue, constructive worry, and behavioral experiments[118, 119].

Our decision to use BT as first-stage and CT as second-stage therapy (rather than a full CBT package introduced at once) was guided by several factors. First, BT is a brief intervention that can be implemented in most clinical settings, thus, enhancing its transferability to clinical practice. In contrast, CT is more time consuming and may not be essential for many with insomnia. Yet, because of its unique features in targeting some cognitive perpetuating mechanisms (e.g., worries, ruminations, low mood, self-monitoring) shared by insomnia and some comorbid psychiatric disorders (e.g., anxiety, depression), use of CT separately from the BT component will provide an opportunity to evaluate its unique contribution to outcomes among those with and without comorbid psychiatric disorders. We expect CMI patients to have a better response to this cognitive intervention. This innovative feature is also likely to make the switch within the psychological treatment modality (i.e., from BT to CT) more equivalent conceptually to the switch within the pharmacotherapy modality (i.e., from zolpidem to trazodone). These second stages therapies may have a broader mechanism of action in addressing sleep and mood symptoms relative to BT and zolpidem that target only sleep.

Medication (MED). The first-stage pharmacological treatment involves zolpidem, 5 to 10 mg, taken nightly at bedtime for the 6-week duration of first stage treatment. The primary factor leading to the choice of zolpidem as a first-stage therapy is that it has consistently been among the most commonly prescribed medications for treating insomnia and its efficacy as an insomnia therapy is well-documented[43, 44, 120]. It also has efficacy for treating the insomnia of depressed patients treated also with antidepressant medications[121]. The primary concern about zolpidem is that it has established efficacy mainly for sleep onset difficulties but only limited evidence showing its benefit for sleep maintenance problems[121]. Yet, we believe that the other considerations outweigh this one. Despite reports highlighting its behavioral side effects, including sleep eating, sleep walking, and other complex behaviors, these events are not specific to zolpidem, and are at least partly related to additional factors (e.g. excessive doses, combination with alcohol or other medications, and sleep deprivation). Enrollees will be advised about each of these. Zolpidem is preferable to alternatives such as eszopiclone and temazepam, which have longer half-lives and greater potential for morning sedation and shorter-acting drugs such as zaleplon and ramelteon, which are less likely to reduce WASO.

Participants will start with an initial dose of 5 mg, in consideration of our participants' age range and the desire to minimize potential side effects. The physician may adjust the dosage between 5 mg and 10 mg depending on the patient's age, therapeutic response, and side effects. Support and encouragement to comply

with the prescribed medication regimen will be provided, but no BT or CT interventions will be allowed during these sessions. The physician will use a treatment manual specifically developed for this study, designed to standardize administration of the medication. All medications will be dispensed by the pharmacy at each site.

The second-stage pharmacotherapy will consist of trazodone (50-150mg), taken 30 minutes before bedtime. We chose trazodone because it is also among the most commonly prescribed medications for insomnia in clinical practice[43, 44]. It has shown efficacy for insomnia occurring with major depression, and it is the most commonly administered treatment for this problem by psychiatrists[45-47]. Admittedly very few studies have been conducted with this medication and it has only short-term (e.g. one week) efficacy in primary insomnia[122]. Nonetheless, testing trazodone's efficacy for insomnia is an important endeavor. As noted in the 2005 NIH state-of-the science conference on the manifestations and management of chronic insomnia summary report: "..., the antidepressant trazodone is now the most commonly prescribed medication for the treatment of insomnia in the United States. In short-term use, trazodone is sedating and improves several sleep parameters. All antidepressants have potentially significant adverse effects, raising concerns about the risk–benefit ratio. Moreover, there is a need to establish and communicate to prescribers dose-response relationships for all of these agents"[85].

c.8. Treatment Implementation/monitoring

First-stage and second-stage treatments. The first-stage psychological treatment, BT, will be administered in the context of four, individual, 45-min sessions led by a trained therapist (clinical psychologist) spread over the 6-week period (i.e. Weeks 1, 2, 4 and 6). The first stage medication therapy, zolpidem, will be administered by a physician in the context of four, similarly scheduled individual, 20-min consultation sessions over the same 6-week period. Participants who do not remit with first-stage therapy will be encouraged to continue with second-stage therapy also implemented in the context of four, individual, consultations visits. Participants in full remission after first-stage therapy will continue on their initial treatment regimen and receive no further therapy visits, except for monthly adverse event monitoring via phone and the regularly scheduled follow up visits. For example, those treated with medication will continue receiving the study medication and BT participants will be instructed to continue using the procedures they learned during the initial treatment phase. Our past studies suggest roughly 40% of enrollees will remit with initial treatment and 60% will continue suffering clinically significant insomnia making them eligible to continue into a second-stage therapy.

Therapists and treatment manuals. Trained clinicians will deliver treatments guided by therapy manuals. Clinical psychologists will administer BT and CT, and physicians will administer medications. All therapists will receive training at a central site (Laval University) and will meet minimal competency criteria prior to treating study participants. The BT/CT manual will be modeled after published therapy manuals[32, 119, 123]. The pharmacotherapy manual will be based on those used in our previous studies of insomnia medication.

Treatment fidelity checks. All therapy sessions will be audio-taped and a random portion (15%) will be rated with standard checklist by blinded raters for the presence of essential ingredients of a given treatment and for the absence of proscribed treatment instructions. Clinicians who fail to meet criterion will receive additional training and, if unable to meet minimal competency criteria, they will be replaced. Participant's performance will be evaluated using periodic drug/alcohol screens, therapist ratings of BT and CT adherence (e.g., time spent in bed) and/or use of study medications (e.g., frequency and dosage), and weekly pill count.

Drug tapering. At the end of treatment, participants on medication will receive a last medication supply and a written withdrawal schedule (designed by study physician) for the subsequent 2-3 weeks. They will be informed of possible rebound insomnia and instructed not to discontinue medication abruptly. The time individuals require for discontinuing medication may vary, yet a 2-3 week taper should be adequate for most. A similar schedule will be followed for those using trazodone during second stage treatment. Those staying on medication through follow-ups will use a similar discontinuation schedule at the end of the 12-month follow up. Those who wish to continue medication will be referred to their primary care physician for further follow-ups.

c.9 Data Management and Analyses

This section was revised based on the useful critiques from the Summary Statement. For instance, expected attrition rates were revised upward and better justification is provided based on previous studies using similar treatment conditions (and no placebo control). Strategies to examine the impact of missing data, specifically MAR or NMAR, are specified and power estimates were recomputed accordingly. Linear mixed models were replaced with weighted generalized estimating equations when appropriate (Aim 2 analyses) and sensitivity analyses are planned to capture the uncertainty of some parameters (attrition, covariance structure). Statistical analyses will be performed and reported according to the CONSORT guidelines[124]

Randomization. Equal numbers of patients will be randomly assigned to the two stage-one therapies (n = 160 to BT, n = 160 to zolpidem), stratified by clinical site. Random block sizes of two and four will be used to insure balance while minimizing the probability of identifying the assigned condition. Assignment to treatment will be determined by a computer-generated random allocation schedule. Sealed, consecutively numbered envelopes with treatment assignment will be used to conceal randomization. Once a patient is eligible for study inclusion, an envelope with a pre-determined group assignment will be opened by the study coordinator. After completing stage one therapy, only patients who do not remit and consent to enroll in stage two will be randomized to a second stage treatment: (1) those not remitting with BT will be equally assigned to either zolpidem or CT, and (2) those who do not remit with zolpidem will be assigned to either BT or trazodone.

Data Management. We will use direct data entry tools (tablet PCs and IVRS diaries) when feasible to minimize data collection errors and facilitate data management. Paper-based data collection will be entered at each site in an Access database by two independent assistants. Dr Ivers (statistician) will revise data periodically to identify missing or incoherent data. Weekly reports about completion rates will be mailed to each PI for study monitoring. Computerized data entry and ongoing revision of all data collected on-site will reduce missing data. We will investigate missing data patterns to ascertain if data are missing completely at random (MCAR), at random (MAR) or not at random (MNAR)[125]. Guided by experts on longitudinal data analysis with missing data[126] and a recent review of 48 RCT datasets from 25 NDA submissions of neuropsychiatric drugs[127], our primary analyses will use statistical models that are robust to MCAR and MAR patterns. However, we will perform sensitivity analyses for MNAR considering specific reasons for attrition if needed[128]. No data imputation will be performed and all available observations will be included in inferential analyses.

Data Exploration. Descriptive statistics will be used to summarize all study variables. We also will construct plots of longitudinal outcome variables to understand their general trends over the study period. We will examine all variables to determine if parametric distributional assumptions are valid. Because the inferences in our analyses are robust to departure from normality, no transformations will be made if the variables are approximately normal. Sociodemographic, psychiatric, medical, and sleep characteristics will first be described using central tendency and dispersion indices for continuous variables, and frequency distributions for nominal data. To confirm the balanced randomization, treatment conditions will then be compared using appropriate parametric or non-parametric tests.

Primary Outcome Analyses. All primary outcome analyses will be conducted based on the Intention-to-Treat (ITT) principle. Accordingly, all patients with at least one post of baseline data will be included in these analyses. To control for possible site effects, clinical site will be included as a main effect and the inclusion of a clinical site interaction with other main effects (when appropriate) will be investigated for significance.

Hypothesis 1a. The proportion of patients achieving remission with first-stage therapy and sustain remission through follow-up will be higher among those receiving BT than among those receiving zolpidem. A standard logistic regression will be used to compare the probability of short-term (after Stage I treatment) and sustained remission (primary outcomes) between BT and zolpidem conditions. Sustained remission is defined as an ISI score < 7 observed after Stage 1 therapy and maintained at (12 weeks and the 12-month follow-up).

Hypothesis 1b. A lower proportion of the CMI patients will achieve remission with first stage therapies than will those with PI. A similar logistic regression will be used to compare the probability of short-term (after stage one treatments) and sustained remission (primary end point) according to the presence of psychiatric comorbidity. This effect will be investigated as a moderator of the impact of stage one treatment on remission. The significance of a moderator is presumed by a significant moderator X treatment interaction[129]. To investigate the moderating effect of psychiatric comorbidity, this variable and its interaction with treatment will be added as fixed effects to the logistic regression model. A significant interaction then will be explored using simple effects to test if CMI is associated to poorer acute and long-term outcomes for each stage one therapy.

Hypothesis 1c. Secondary outcomes (PSG, sleep diary, fatigue, mood, etc) will show greater improvements through treatment and follow-up for those receiving BT than for those receiving zolpidem. Comparisons between these therapies for secondary outcome measures will be performed using a mixed model approach[130], including a generalized mixed-effect regression models for binary variables (e.g., diagnosis for insomnia) and a normal mixed-effect regression models for continuous variables. In both modeling approaches, treatment, time and potential confounding factors will be included in the models as fixed main effects. The models will also include random effects for intercept and slope (patient by time) for each subject.

Hypothesis 2a. The insomnia remission rate after second-stage treatment for all conditions combined will be 20% higher than with first-stage treatment (i.e., increment from 40% to 60%). Since participation in the

second randomization is conditional upon not remitting with first-stage therapies, generalized estimating equations models (GEE) will be used to test whether overall remission rate significantly increased. GEE is a semi-parametric statistical approach that provides robust empirical estimates by avoiding full specification of the joint distribution of outcomes. The weighted GEE approach[131] will be preferred in this trial to take into account the missing data pattern (MCAR or MAR).

Hypothesis 2b. Of all patients who enter second-stage treatment, a greater proportion who switch modalities (i.e., BT→zolpidem or zolpidem→BT) will achieve remission and sustain it through follow-up than will those staying within a treatment modality. To maximize degrees of freedom, weighted GEE models will be used to compare remission rates after 12 weeks of treatment and sustained remission after 12 months, according to two main effects: (a) having received BT or zolpidem during Stage I and, (b) having switched treatment modality or not during Stage II. These main effects and their interactions will capture the partial effect of each treatment combination while accounting for relevant patient trajectory (data from Stage I & Stage II therapies). Other main fixed effects (e.g., time) and potential baseline covariates will be included. Weights will be computed for each case after specifying a drop-out model estimated from the observed drop-out patterns.

Hypothesis 2c. CMI patients who enter second-stage treatment will show a higher remission rate with treatments that target sleep and mood symptoms (e.g. CT and trazodone) than with treatments targeting primarily sleep (BT and zolpidem). This added therapeutic effect will be higher in CMI than in PI patients. Two tests will be of primary interest within the full factorial (comorbidity x conditions x time) weighted GEE model: (a) an a priori contrast to examine remission rates after stage two treatment according to whether CMI patients received the "mood addressing" sequences (BT→CT or zolpidem→trazodone) or the "non-mood" sequences (BT→zolpidem or zolpidem→BT); (b) a comorbidity x treatment interaction will be used to compare whether the added therapeutic effect obtained by addressing mood symptoms is higher for CMI than for PI patients. Significant interactions will be examined with simple effects to test whether temporal changes observed for each subgroup during second-stage therapies are significant. Other fixed effects such as first-line therapy and potential baseline covariates will be included.

Hypothesis 2d. Secondary outcomes will show response patterns consistent with Hypotheses 2a-c. Analyses related to these hypotheses will be based on the scale of measurement. When the outcomes are assessed on a binary scale, identical analyses will be performed. When the outcome are assessed on a continuous scale, weighted GEE will be specified with a normal distribution and an identified link function.

Sample Size and Detectable Effect Size. All sensitivity power analyses were computed following procedures outlined by Stroup[132] for mixed models and Dahmen et al.[133] for weighted GEE models, and were based on standard conditions: a two-sided alternative hypothesis, 80% power, and a type I error rate of 5%. Based on studies conducted by our group [2, 134, 135], and recent reviews of the literature on this topic[136], attrition rates of 10% for BT/CT conditions and 20% for zolpidem/trazodone conditions during stage one and two therapies, and 10% at 12-months follow-up were used as attrition estimates in the computation of detectable differences. We recognize this limitation, but lack of preliminary data on primary and secondary outcomes precluded computation and further inclusion of random outcomes variance in the power computations[137].

Hypothesis 1a: Assuming a one-tailed directional hypothesis (BT > zolpidem for remission), our sample size of 320 will give a standard power to detect a difference of 14.7% in sustained remission between BT and zolpidem.

Sensitivity analyses for Hypothesis 1a

Sample size per group	120	140	160	180	200
Detectable difference in remission rate	17.2%	15.9%	14.7%	13.9%	13.2%

Hypothesis 1b: Since this hypothesis is tested using a similar analytic strategy as H1a, very similar detectable differences are observed in power computations and thus are not reported here.

Sensitivity analyses for Hypothesis 1b

Sample size per group	120	140	160	180	200
Cohen's f (small = 0.10)	.076	.071	.066	.062	.059
Detectable difference in SOL (min.)	4.8	4.5	4.2	3.9	3.7
Detectable difference in WASO (min.)	5.5	5.2	4.8	4.5	4.3

Hypothesis 1c: A sample size of 320 (effective sample = 272) would give a standard level of power to detect a small effect size (Cohen f = 0.066) on the condition (BT vs. zolpidem) X time (baseline vs. Post-I) interaction. Translated into clinically relevant units (based on variability estimates from Morin et al., 2009), this

Sensitivity analyses for Hypothesis 2a

Sample size per group	120	140	160	180	200

sample size would allow the detection of a difference of 4.2 minutes of SOL and 4.9 minutes of WASO between temporal changes observed in the BT condition vs. those observed in the zolpidem condition.

Hypothesis 2a: A sample size of 320 (effective sample at Post 2 = 234 after taking into account attrition) will give a standard power to detect a increment of 8.2% in remission rate between Post I and Post II assessments, assuming a working correlation of 0.50.

Hypothesis 2b: A sample size of 320 (effective sample at Post 2 = 139 after attrition and after the second randomization on about 60% of the remaining sample) will give a standard level of power to detect a 28.6% difference in remission between patients who switched treatments and those who did not, and sufficient power to detect an increase in remission rate of 20.5% for patients who switched treatments.

Sensitivity analyses for Hypothesis 2b

Sample size per group	120	140	160	180	200
Detectable difference in remission rate for interaction effect	32.3%	30.7%	28.6%	25.3%	22.8%
Detectable difference in remission rate for time effect (switchers)	25.3%	22.7%	20.5%	18.1%	16.1%

Hypothesis 2c: Since this hypothesis is tested on the same sample size than H2b (effective sample at Post 2 = 139 after attrition and after the second randomization on about 60% of the remaining sample), similar levels of power and minimally detectable differences are expected. Results are thus not reported here.

Hypothesis 2d: This hypothesis is tested using the same analytical procedure as for H2a-H2c but it is completed with continuous data wherein baseline data can be included. These tests are much more powerful. For a sample size of 320, all detectable Cohen's f values are found to be less than 0.10 (e.g., a difference of 7.5 min on SOL between switchers or non-switchers, or between mood-addressing or not modalities).

4. HUMAN SUBJECTS

4.1.1 Risks to Human Subjects

a. Human Subjects Involvement and Characteristics: Human study participants will provide personal information about themselves both through interviews with project staff and through completion of questionnaires. The various procedures they will undergo have been outlined in detail in the preceding section. Across our two study sites we plan to enroll a total of 320 persons with insomnia who are mentally competent and without life-threatening diseases or serious psychiatric illnesses that warrant immediate clinical attention. Individuals $\geq$ 21 years of age will be enrolled in the study if they agree and meet entry criteria. The anticipated demographic characteristics of our sample are described below (see section **E6 Inclusion of Women & Minorities**).

b. Sources of Materials: Prospective subjects will undergo screening procedures including a phone screening, a clinical interview, sleep diary monitoring, a medical exam, (including routine lab tests), a structured clinical interview for DSM-IV diagnoses (SCID) and a Structured Interview for Sleep Disorders (DSISD). If results of these screening procedures favor inclusion of the study candidate, a laboratory PSG study will be conducted to rule out sleep apnea and periodic limb movement disorder. Some of the participants will be sleep clinic outpatients who initially present to one of our site's sleep clinics seeking treatment for their insomnia. For these patients, any existing clinical data collected within 3 months of study entry including sleep diaries, sleep history information, results of medical examinations, and available PSG findings will be considered for use as the screening measures should the study candidate agree to this and sign proper release forms so such information can be released to project staff. Those study patients accepted into the study will complete: (a) various questionnaires prior to treatment, during therapy, at the end of treatment(s), and at follow-up; (b) sleep diaries before treatment, during treatment(s) and at various follow-up assessment periods; (c) two pre-treatment and four post-treatment PSGs (maximum six PSGs); and (d) interviews with a blinded clinical rater before treatment, at the end of treatment(s) and at 3-, 6-, 9- and 12-month follow-up time points.

c. Potential Risks: During the course of the study, study patients will experience a degree of inconvenience and disruption of their usual routines while they undergo various assessment procedures. A small percentage may suffer temporary skin irritation from adhesive materials used during PSG recordings. Participants will be asked to complete questionnaires that ask probing questions concerning mood and habits. Some persons could find these questions unsettling. Furthermore, there is always a risk of accidental disclosure of the psychological and medical information recorded and maintained. In addition, there are the typical risks associated with blood drawing (i.e., discomfort and/or bruising, infection, excess bleeding, clotting, or fainting) conducted as part of the qualifying medical evaluation. Finally, there are risks of side effects or adverse events from taking the various medications that could be prescribed in this study. Zolpidem is approved by the FDA for the treatment of insomnia. Common side effects (occurring in 1% to 25% of people [1 to 25 out of 100 people]) associated with zolpidem 10 mg used for up to 35 days include headache, drowsiness, dizziness, allergy, dry mouth, back pain, lethargy, and a "drugged" feeling. Sleepiness or drowsiness related to zolpidem could increase risk of accidents while driving or at work. Rare side effects (occurring in less than 1% of people [1 out of 100 people]) include arthralgia (pain in a joint) and hypomania (feeling "speeded-up", thinking or talking faster than usual). Zolpidem is listed in Pregnancy Category B.

Trazodone is approved by the FDA for the treatment of depression, but it is not currently approved for the treatment of insomnia. In this study we will use a lower dose of trazodone (50-150 mg) than has been used in published studies for the treatment of depression (200-600 mg). Common side effects (occurring in 1% to 25% of people [1 to 25 out of 100 people]) associated with trazodone at typical antidepressant doses include insomnia, diarrhea, headache, migraine, dry mouth, somnolence, ejaculation disorder (primarily ejaculation delay), dizziness, increased sweating, constipation, fatigue, indigestion, flu-like symptoms, decreased interest in sexual activities, decreased appetite, rhinitis, sinusitis, abdominal pain and impotence. Sleepiness or drowsiness related to trazodone could increase risk of accidents while driving or at work. Trazodone is listed in Pregnancy Category C. Potential study participants will be informed of the FDA's warning about of the risk of suicidality associated with antidepressants during the consent process. This warning will be specified in the consent form presented to insomnia participants.

In addition, there may be unanticipated side effects related to taking medications prescribed in this study, particularly if the study drug is taken in combination with other medications. Throughout the study, subjects may take medications they are instructed not to take by the study staff. This includes prescription medicines as well as herbal substances or over-the-counter drugs. The risk of a drug interactions and

reactions is always a possibility. There may be medications that some individuals are taking that they will have to stop taking in order to participate in this study. Stopping some medications can cause withdrawal symptoms or other side effects. For females of reproductive potential, taking the study drug while pregnant could expose an unborn child to significant risks.

Participants may experience treatment-specific side effects if they receive BT. Side effects associated with BT may result early in treatment as a function of limiting a subject's time in bed (TIB). Initial TIB restrictions may, in some patients, lead to enhanced daytime sleepiness. This enhanced sleepiness may place some study patients at increased risk for accidents while driving and, thus, it will be necessary to instruct them to limit their driving during the early stages of BT. Also, some study patients may become alarmed by this sleepiness and may drop out of treatment. However, patients usually respond positively to our education and support when delivering BT so our treatment dropout rates usually remain low. Once study patients enter the treatment phase of the project they risk assignment to an active treatment that they find less than optimal.

4.1.2 Adequacy of Protection Against Risks

a. Recruitment and Informed Consent: Study participants will be recruited from our outpatient sleep disorders clinics, ongoing clinical trials, flyers posted throughout our medical centers and academic departments, and print or broadcast advertisements. Prospective study participants in our outpatient clinics will be approached by one of the PIs or a member of the research staff, informed of the study, and questioned about their willingness to participate. Those interested will be provided the telephone number of the project coordinator (PC) so they can pursue enrollment. Those responding to advertisements will obtain the PC's phone number in the published advertisement. Clinical patients who show interest in enrolling as well as all who respond to advertisements will initiate a telephone contact with the PC who will provide a thorough description of the study and its requirements, and conduct an initial brief phone screening. During the first in-lab screening visit, the PC will review the consent form with the study candidate and answer all of the participant's study-related questions before the participant is asked to sign the consent form. Once the consent form is signed, a formal mental status examination will be administered to determine the participant's capacity to provide consent. Should results of this mental status screening show the participant in question is not competent, she/he will not be allowed to continue in the study.

b. Protections Against Risk: This investigation has been designed to minimize the risks and discomfort incurred by study patients. Efforts will be made to reduce inconvenience to participants by scheduling assessment and treatment sessions at times that are most convenient to them. There is a reduced risk of physical harm resulting from this study since those with serious medical illnesses or unstable psychiatric conditions will not be enrolled In addition, there will be no inclusion of children, mentally impaired persons, or prisoners in this project.. Students and/or Staff at National Jewish Health may also be patients at the National Jewish Health Sleep Center. If they meet the study criteria they could potentially be recruited in our study. If a National Jewish Health student or staff member volunteered to take part in this study all of their protected health information and study data are de-identified, only the Prinicipal Investigator and study coordinator and the study sponsor would have access to the key. All files with protected health information and study data are kept in separate files in locked cabinet in locked rooms at all times. We will follow all HIPAA and National Jewish Health guidelines about protecting patient confidentiality. Students or staff reporting directly to the Principal Investigator, Jack Edinger, PhD will not be eligible to participate in this study.The PC will follow-up SCID or other interview/questionnaire findings that connote imminent suicide potential or an unstable psychiatric condition, and provide appropriate referrals or intervention. In the event that a participant finds the questionnaires disturbing, the site PI will be available to speak with the participant. The PC will have a graduate degree in clinical psychology, social work, nursing or related healthcare field and will have clinical experience in conveying appropriate empathy for concerns and guidance to participants when dealing with emotion-related information. At each study site, the PC will be trained by the site PI to handle personal material with confidentiality and sensitivity. The PC will need to show certification of completion of ethics courses in dealing with human subjects and issues relating to drug trials prior to having contact with any study participants.

In our experiences, the few occurrences of temporary skin irritation from adhesive materials used during PSG evaluation are minor, short in duration, and often can be prevented or minimized by use of hypoallergenic adhesive materials. Since the participants enrolling in this trial are complaining of a sleep disorder, it would not be uncommon for some of them to undergo a PSG as part of their "real-world" assessment. Thus, they are not subject to an unusual risk by participating in the study and undergoing PSG monitoring.

Adverse events will be monitored at each therapy visit and standard procedures will be followed whenever an adverse event is recorded. We will continue to monitor those who remain on the study medication after completing their regular weekly therapy visits at each of the follow-up visits, as well as with a monthly phone call made between each follow up visit. We anticipate that we will be able to effectively manage the above-mentioned treatment-related side effects throughout this trial. Our study physicians have extensive experience with the medications to be employed in this trial and are well able to manage the side effects that may emerge. Participants in all conditions will be seen weekly during the acute treatment phase(s) by the Study Physician, During the follow-up phase, they will have contact with study staff on a monthly basis either via phone or for the planned 3-, 6-, 9- and 12-month follow-up assessments. Since study physicians will have some options to adjust medication dosages during the acute treatment phase, side effects may be minimized by use of the lowest effective doses of the study medications prescribed. Should medication side effects prove intolerable in the first tier treatment, patients may be switched to an alternate medication or psychological therapy in the second stage. Also, patients will be allowed to withdraw from the trial should they have undesirable effects from the medication(s) they are given. A study physician will closely supervise discontinuation of all study medications. Study staff, including physicians, will be available at all times by telephone or in person to address any adverse events or questions that arise during the course of the study.

To protect women of reproductive potential from risk due to the medication, pregnant women, women who are breastfeeding, or those who plan to become pregnant during the study will be excluded from study enrollment. For women of childbearing potential, a urine pregnancy test will be conducted, and must be negative before their entry into this study. If sexually active, women must agree to use appropriate contraceptive measures for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization, (2) approved hormonal contraceptives (such as birth control pills, Depo-Provera, or Lupron Depot) in combination with a barrier method, (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Women participants will be instructed to inform their study doctor immediately if they become pregnant during the study at which point participation in the study will end. The study doctor will then track the pregnancy and report the outcome to the Institutional Review Board (IRB).

We recognize that some study participants may choose to use non-study medications (prescription or OTC) as sleep aids despite receiving instructions not to do so. In addition to their confounding effects on study results, such practices could result in AEs due to interaction of these medications with those medication therapies provided by this trial. Both to discourage and detect such practices, we will conduct random urine drug screens twice during each treatment phase (first- and second-stage therapies) with each participant. These urine screens will occur during scheduled visits with a study therapist or physician. Participants who voluntarily report use of non-study sleep aids on more than two occasions (nights) while in the study and those who fail to report such use but test positive for non-study prescription sleep aids on a urine drug screen will be discontinued from the trial. However, we will retain all data even from subjects with protocol deviations. These protocol violations will be documented by creating a dummy variable (yes/no) for these subjects. The dummy variable will be included in the statistical models to test for significance and to control for its potential influence on all comparisons of interest.

Our experience shows that patients' concerns about BT side effects can be effectively managed by education about potential sleepiness and supportive encouragement during individual treatment sessions. Additionally, as study patients determine their optimal time in bed, their reports of sleepiness decrease. Problems with BT–related side effects should be minimized in this trial since the therapists who will administer this treatment will have structured training and PI supervision (Drs. Morin & Edinger) in regard to administering this form of therapy.

Protection of confidentiality will be accomplished by assigning each participant a distinct research code number and using this code number rather than the person's name on all documents and electronic data acquired from that individual. Data acquired from all participants will be kept in locked files at the study site, and only this project's staff will have access to these files. When data are transferred for use in the planned analyses, these data sets will include only participants' research code numbers as identifiers and they will be encrypted prior to electronic transfer to the data center (Ivers – Laval site). No names or other unique identifiers will be included in any of the data sets used in the planned analyses of this project. Furthermore, all data will be encrypted before it is transferred electronically to the data center for analyses.

Given our plan to enroll patients with comorbid insomnia (CMI), it is possible some such patients may have or develop an unstable comorbid condition that could make enrollment or continuation in this study undesirable. Our plan is to enroll only those CMI patients who have insomnia in the context of an associated

stable psychiatric condition. We have included extensive screening procedures to exclude those with unstable comorbid conditions. As an added risk management strategy, we will consult prospective subjects' treating physicians and seek their permission/endorsement of the subjects' enrollment in this study. Should a patient with stable medical/psychiatric condition at the time of enrollment, show a worsening of the associated condition or develop a new condition that may make their continued study participation risky or unwise, the participant will be evaluated by the study physician and the subject's treating physician(s) will be consulted. Should either the study physician or the treating physician decide that continuation in the study is medically/psychiatrically contra-indicated, the study subject will be immediately removed from the trial and referred back to the treating physician or a physician of the subject's choice for appropriate medical/psychiatric management. As above, study staff including physicians will be available at all times to address and manage medical/psychiatric concerns that arise during the course of the study.

Admittedly this project presents a degree of burden to participants, as it involves about 14 months of study involvement with multiple appointments and periods of daily monitoring. We have attempted to minimize this burden by only including those measures that would be most valuable and by deriving a compensation schedule commensurate with the amount of time participants will spend completing study procedures. In addition, given that we will recruit from our clinics and ongoing trials, it may not be necessary for such study patients to repeat screening measures (i.e., medical examination, 2 nights of PSG, or sleep diaries) if these measures were completed in our clinic/laboratory within the past 3 months and such patients provide proper written consent to release such information to project staff for use in their screening. It is unlikely that there will be any significant changes in their eligibility on these measures and we have found that asking participants to repeat these procedures so soon after they have completed them can unnecessarily impede recruitment. In addition to preventing unnecessary burden, using existing data is also a cost-effective solution. However, use of such pre-existing clinical information will be left up to each participant, and those who prefer to not release this information will be asked to complete all listed screening procedures de novo for this project.

4.1.3. Potential Benefits of the Proposed Research to the Subjects and Others

It is estimated that study patients will be provided assessment/treatment services that would cost several thousand dollars if provided on a purely clinical basis. Participants will benefit from a free and comprehensive insomnia diagnostic evaluation and receive CBT and/or pharmacological treatment free of charge. Participants will be provided monetary compensation to cover their parking expenses and the time and effort they will invest completing the various study procedures. To minimize the problem of attrition due to participant burden, there will be incentives for completing study procedures conducted for screening or outcome assessment. The table below outlines the projected time commitment and compensation to be provided for the various study-related assessment procedures. As shown, patients will be compensated for all assessment procedures from the screening phase through the final 12-month follow-up. We believe the level of compensation to be provided is reasonable given consideration of the relative burden involved. The reimbursement rates across the study should be sufficient to maintain a reasonably high retention rate throughout the study including the follow-up period. Hence, we anticipate a large proportion of those who complete treatment will return for follow-up. The clinical cost savings and the compensation they will receive are a benefit to study participants. Previous studies have shown that insomnia is effectively treated with CBT

REIMBURSEMENT SCHEDULE

Study Procedures	Estimated time per activity	Reimbursement per occasion	Total occasions	Maximum Compensation
Screening interviews, sleep diary, medical exam	75 min.	$35.00	1	$35.00
PSG	8-9 hours	$30.00	4-6	$180.00
Sleep diaries before, during and after treatment(s)	15 min./week	$10.00	24 weeks	$240.00
Outcome Questionnaire Battery	45 min.	$30.00	7	$210.00
Clinician Interview for ISI, CGI and RDC Ratings	20 min.	$20.00	7	$140.00
Medication monitoring visits during follow-up	15 min./month	$15.00	4	$60.00
Grand Total	---	---	---	$865.00

and the study medications provided so those insomnia patients randomized to active therapy have a good chance of deriving clinical benefits. Those who do not appreciate improvement in sleep will be provided with referral services. Furthermore, many of those insomnia patients enrolled may be pleased by the notion that they are contributing to research that might improve treatment practices for their disorder.

4.1.4 Importance of the Knowledge to be Gained

Insomnia patients typically present with a complex array of symptoms including sleep difficulties, fatigue, and mood disturbances. As noted in the **Background and Significance** section, this application addresses research priorities clearly set forth in the 2005 NIH State-of-the-Science Conference on the Manifestations and Management of Chronic Insomnia in Adults. As noted in the summary statement from that conference, "...little is known about the comparative benefits of these treatments, their combination, and their effects on understudied features of chronic insomnia. To address this lack of knowledge, randomized controlled trials will be required that are large scale and multi-site and compare at least two effective or promising treatments. This should include comparisons between pharmacological agents as well as between those agents and CBT." This multi-site trial is specifically designed to address such objectives and to test such treatments in patients with both primary and co-morbid forms of insomnia. The proposed study is also responsive to PA-07-092, "Collaborative R01s for Clinical And Services Studies of Mental Disorders, AIDS and Alcohol Use Disorders (R01)."

Currently there are few data available concerning the relative efficacy of the psychological/behavioral and BzRA therapies for managing primary and comorbid insomnia since large multi-site head-to-head comparisons of these treatments have yet to be conducted. Furthermore, there are virtually no data on the how well each of these treatment approaches perform in producing and sustaining insomnia remission over time. Finally, the value of sequenced treatments for patients who fail to achieve insomnia remission when BT or BzRA are used as first-line therapies has yet to be thoroughly explored. We have designed the project proposed to address these major deficits in the insomnia treatment literature. Given the previously discussed prevalence, morbidity, and societal costs of insomnia, the knowledge to be gained from this project is immensely important to insomnia sufferers themselves and to society at large.

We believe this project holds great promise for providing important new information that will be important to practitioners and researchers who work with insomnia patients. Such research appears directly in line with the above-mentioned recent NIH statement that calls for investigations comparing pharmacological and behavioral treatments for primary Insomnia and for testing these therapies among patients with insomnia occurring comorbid to psychiatric conditions. Our planned project holds the promise of optimizing treatment for an under-researched and under-serviced group – those with comorbid insomnia. In addition to the value of the planned primary analyses detailed in the **Data Management and Analyses** section, the data collected for this project will be used to explore other research questions. For example, we will be able to ascertain how insomnia type (PI vs. CMI) moderates treatment outcome. We will also be able to examine the degree to which changes in traditional sleep-specific outcome measures (e.g., derived from diaries and PSG) predict overall insomnia remission status and improvements in measures of diurnal functioning. This trial will also provide us an initial opportunity to test the utility of global insomnia RDC as an insomnia treatment outcome measure. The rich data set acquired in this project will, thus, provide opportunities for exploring many important questions in addition to the **Objectives/Hypotheses** outlined as our **Specific Aims**.

4.1.5. Data & Safety Monitoring Plan

Since the project proposed entails conducting a large clinical trial, it requires a Data and Safety Monitoring Plan (DSMP). Therefore a general DSMP has been developed for this project. Given the size and nature of this project, we will solicit the services of three prominent clinician/scientists (to be named), to serve as the Data and Safety Monitoring Board for this project. The PIs will consult with NIH and seek advice from program staff in identifying individuals best suited to serve on the DSMB for this project. However, we will attempt to select DSMB members who have extensive experience conducting clinical trials and who are very familiar with the methodology they entail. Also, through their professional training, clinical practice, and research experience, they collectively should have sufficient knowledge of insomnia disorders, behavioral therapy techniques, and pharmacological agents to allow them to adequately evaluate the data and safety issues specific to this clinical trial. Neither the PIs nor any of the collaborating investigators will have had any significant professional collaborations or close personal relationships with these individuals. Hence, there will be no conflicts of interest between the project staff and the DSMB members that would interfere with them

carrying out the DSMP.

The DSMB will convene annually for a conference call to review ongoing study procedures, discuss AEs and other safety issues, and to evaluate ongoing methods for maintaining data integrity and confidentiality. Should the DSMB develop any concerns on the basis of information provided to them by the PIs, they may request to examine hard or electronic copies of participants' research records from either of the study sites. In transferring such information to the DSMB, participants' identities will be protected by transferring only data that are de-identified (hard copies) and/or encrypted (electronic data). In considering the frequency of meetings, we have tried to strike a proper balance between maintaining participant safety and the integrity of the study, and the consequent time, workload, and cost to the study budget in preparing reports. Traditionally, DSMB convene once a year unless there are compelling reasons why they should meet more often. We believe that, in the case of this trial, annual meetings will be sufficient. However, to ensure safety, we have opted to submit annual reports to the DSMB that detail enrollment, attrition, and safety assessment information. These reports will permit close monitoring of the trial and the DSMB will retain the option of making a site visit if they have concerns that are not addressed via telephone. In addition, two-weeks prior to the DSMB visit, we will prepare a more detailed report with information pertaining to subject recruitment, accrual, and retention.

In addition, treatment data will be provided either in aggregate for the entire group, or separately by treatment group, in either a blinded or unblinded format, depending on the preference of the DSMB. The statistician who will assess the unblinded data will be unconnected with the day-to-day administration of the protocol. In the report to the DSMB, vital signs and laboratory data will be provided according to range (minimum, maximum, median, and quartile values) and according to whether or not it is abnormal or normal. In addition, the side effect data obtained from the adverse events log and adverse event follow-up interviews will be provided to the DSMB. Aggregate efficacy data will also be made available and, if it is to be presented according to treatment group, then this will again be based upon analyses performed by an independent statistician. Thus, the DSMB will assess safety risks to study subjects, human subject protection efforts, project staffs' adherence to subject confidentially requirements, and the types and numbers of adverse events (AEs) noted during the trial. After each visit, the DSMB will compile the information gained from the monitoring activities and subsequently prepare a report summarizing findings in regard to their monitoring activities. Also included in the report will be their recommendation to continue or discontinue the study. This report will be completed and delivered to the funding agency and PIs in a timely manner, usually within 30 days of the DSMB' meeting. If the DSMB conclude that the study should be terminated, this opinion will be conveyed to the business officials of collaborating sites as well. In the case of this latter type of recommendation, the DSMB will utilize the most rapid method (telephone, telefax) to communicate the unfavorable decision to all relevant parties. Subsequently the PIs, appropriate business officials at study sites, and officials from the funding agency will likely discuss the matter further before a final decision regarding study termination is made.

4.1.6 CLINICALTRIALS.GOV REQUIREMENTS

The current project comprises a clinical trial in which two 1st stage and four 2nd stage treatments for insomnia are compared. Per NIH policy, we plan to register this trial with ClinicalTrials.gov prior to enrollment of any studies participants should this project be funded.

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