Research Strategy

Sleep to Reduce Incident Depression Effectively (STRIDE)

Major Depressive Disorder (MDD) has remained prevalent in the US due to missed opportunities for primary prevention. One solution may be insomnia intervention, as insomnia disorder is a significant risk factor for incident depression. Insomnia also commonly persists despite successful treatment of MDD, and is a predictor of relapse. As a modifiable risk factor for depression, treating insomnia may reduce incident depression; however, a notable barrier is the limited availability of sleep specialists trained in nonpharmacological treatment of insomnia. An emergent solution is the integration of a web-based intervention with primary care services. Along with our preliminary data, studies show that digital cognitive behavioral therapy for insomnia (*d*CBT-I) is an efficacious insomnia treatment, and the use of *d*CBT-I to prevent depression would be novel, widely accessible, scalable and cost-effective for both patients and providers.

We propose a large-scale clinical trial that tests a stepped care intervention to reduce insomnia and prevent depression. This intervention will leverage primary care as a natural entry point for early sleep intervention, and determine the *effectiveness* of a stepped-care model that begins with *d*CBT-I, followed with face-to-face *clinician-based* CBT-I for non-responders. This is an innovative combination of these insomnia therapies with potential for real-world implementation and scalability. Importantly, the trial will also determine the durability of both insomnia treatments over a one year period in order to fully assess the impact on prevention of incident depression and relapse. The goals of this trial will be to 1) determine the relative *effectiveness* of *d*CBT-I alone or in combination with clinician-based CBT-I in non-depressed insomniacs and 2) to test the effects of these sleep interventions for preventing depression incidence and relapse. Moderators of the effects including sleep reactivity, rumination, race, and SES will be assessed.

We will deliver *d*CBT-I to individuals with insomnia disorder, and add face-to-face CBT-I for non-remitters. We will compare sleep outcomes and depression rates to a control group at post-treatment, and then at 1 year follow-up. **Aim 1a)** Assess the acute and long-term effectiveness of *d*CBT-I on RDoC sleep parameters: Insomnia Severity Index (ISI), sleep onset latency and wake after sleep onset in an insomnia cohort including those at elevated-risk for depression (high sleep reactivity, low SES, minority). This aim will be tested by administering internet-based *d*CBT-I to people with insomnia and adding CBT-I in non-remitters (ISI > 10), as well as comparing the RDoC sleep outcomes to an attention control group post-treatment and at 1 year follow-up. **Aim 1b)** Determine the acute and long-term effectiveness of face-to-face CBT-I for insomnia in non-responders to *d*CBT-I on RDoC sleep outcomes (ISI, SOL, WASO) relative to a comparison group post-treatment and at 1-year follow-up. **Aim 2a)** Determine the effects of *d*CBTI and CBT-I using a stepped care model for *prevention* of **2a)** incident depression and **2b)** depression relapse. The 1-year rate of depression of both *d*CBTI and CBT-I will be compared to a control group. **Aim 3a) (Exploratory)** Evaluate changes in nocturnal rumination as a modifiable behavior (post-treatment) that mediates the effect of insomnia treatment on subsequent depression-risk. **Aim 3b) (Exploratory)** Determine the moderating effects of important depression risk-factors (race, SES) on the change in sleep and depression outcomes to establish the critical need and value of early risk-detection and prevention for these groups, and demonstrate the potential greater impact in terms of prevention for individuals with high sleep reactivity.

Figure 1: Study Overview

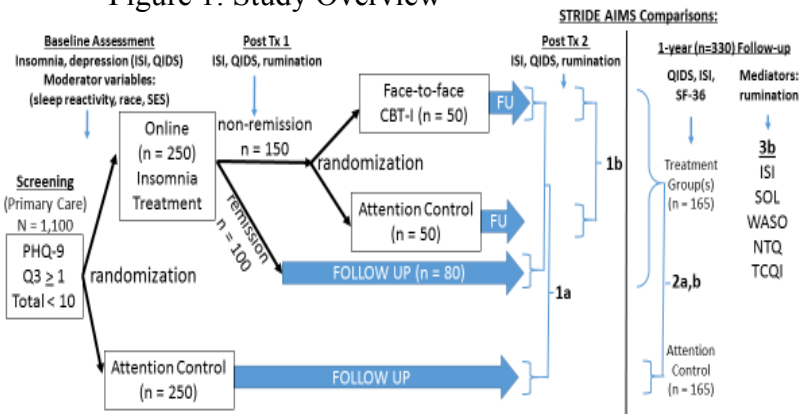
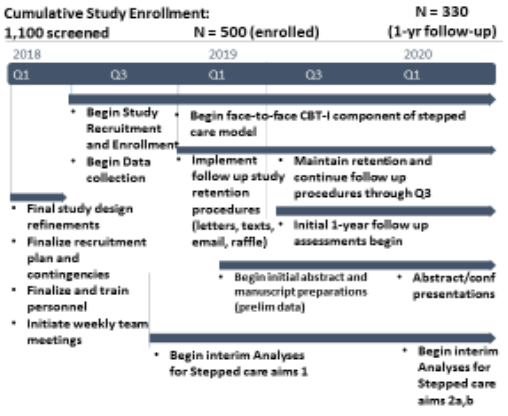


Figure 2: Study Timeline and Milestones



We propose to enroll 500 participants (insomnia without depression) using ongoing data collection procedures within the HFHS network of sites in southeastern Michigan. Baseline assessment will include standardized and validated assessment tools for insomnia and MDD.[9,71,78-82] Following baseline assessment, insomnia participants will be randomized into Insomnia Treatment (T) or Attention Control (C) groups with a sample of no less than 250 per group. The T group will receive 6 weekly treatment sessions via Sleepio (www.sleepio.com), a fully automated media-rich online cognitive behavioral therapy for insomnia *d*(CBT-I).[83] The C group will receive sleep hygiene education, which will serve as a credible placebo intervention as it mimics the web-based patient contact inherent in *d*CBT-I, but is inert with respect to sleep outcomes.[84] As with the *d*CBT-I group, these topics will be divided equally across 6-8 weekly sessions.

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Those without insomnia remission following *d*CBT-I (ISI > 10)[68] treatment (typically 60%) will be randomized to standard face-to-face CBT-I treatment or attention control during this second phase of the SMART design. Treatments will be done at sites spread across the Detroit Tri-county area by psychologists certified in behavioral sleep medicine. For all groups, research assessments (sleep and depression) will be obtained at pre-treatment baseline, post-treatment 1 (~8 weeks following initiation of *d*CBT-I), post-treatment 2 (~8 weeks following face-to-face CBT-I initiation), and follow-up. The 1 year follow-up research assessments will include assessment of depression incidence and relapse occurring at any point throughout the previous 12-month period before the respective assessment. Moderation variables (i.e., sleep-reactivity, demographics) will be collected at baseline and mediation variables (i.e., nocturnal rumination) will be measured at each post-treatment and follow-up research assessment for all groups.

We will align with the recommendations for effectiveness trials, including minimal exclusion criteria to ensure a diversity of the sample representative of the population encountered in clinical practice.[75] We will only exclude those unwilling to participate, under the age of 18, those who screen positive for depression (PHQ-9 or QIDS moderate), those already on antidepressants, those already known to be harmed or not benefitted by one of the CBT-I interventions, known sleep disorders by EMR (e.g. sleep apnea, narcolepsy) and untreated medical or psychiatric disorders.

We assume an overall attrition rate of ~30%. Although trial participants will be predominantly recruited through our network of primary care sites (31 in 2016), we will mitigate recruitment shortfalls through the HFHS Sleep Center patient registry (>20,000 insomnia patients). Participants will receive 20.00 per assessment and follow up.

We will also test treatment effects on quantitative sleep parameters including ISI, sleep onset latency, wake after sleep onset, and sleep efficiency collected using standardized report-based measures. Sleep diary data will be collected during each treatment session to analyze trends across time.[91] Depression outcomes will be measured pre- and post-treatment by the 16-item Quick Inventory of Depressive Symptomatology (QIDS)[77] with insomnia related items removed for analyses (see below). To enter the study participants will need to score less than an 11 on the QIDS. During year 1 follow-up, new onset or recurrence of MDD cases will be identified (QIDS ≥ 13 or a lower sub-threshold of ≥11 for more sensitivity).[77,82]

TARGETS: ***Rumination (mediator)*** refers to negatively-valenced thoughts which increases risk for depression.[93] To test insomnia-induced rumination as a risk factor for depression, we will include a state rumination measure at the post-treatment assessment to be used in a separate mediation model. The target (mediator) is nocturnal rumination assessed using the Thought Control Questionnaire Insomnia-Revised (TCQI).[98] In contrast to healthy sleepers, rumination in insomnia extends into the night.[106] Further, the inability to fall asleep at night can itself trigger negative affective that perpetuate nocturnal rumination.[107] Thus, insomnia may be a key contributor to nocturnal rumination.[108] Yet, no prior study has investigated rumination as a modifiable component of insomnia that when attenuated may lead to reduced MDD risk (Specific Aim 3). ***Sleep reactivity[120] (moderator)*** may also moderate the effects of sleep improvement on depression. **Identifying a significant moderator(s) of treatment impact could inform cost-effective strategies to triage at-risk individuals for depression prevention programs**. This directly aligns with NIMH's Strategic Objective 3, which is to identify focused and impactful *preventative* interventions. One risk factor linked to both insomnia and depression is the heritable trait of sleep reactivity.[122,123] Sleep reactivity is a trait predisposition to insomnia that manifests as a *sleep system* that is over-sensitive or "over-reactive" to stress.[120] The Ford Insomnia Response to Stress Test (FIRST)[124] is a psychometrically and biologically validated instrument used to measure sleep reactivity. It is expeditious and cost-effective, minimizing burden in both research and clinical settings. Substantial evidence demonstrates reliability, validity, and utility for the FIRST. Longitudinal studies have shown high sleep reactivity (FIRST) increase the risk of new onset insomnia and predict the chronicity of insomnia in good sleepers up to 3 years later.[24,132-134]

Aim 1: analysis will be on the post-treatment impact on RDoC sleep outcomes (ISI) and QIDS of the internet-based *d*CBT-I, followed by the more **personalized face-to-face** CBT-I group compared to the attention control group. Quantitative sleep measures, SOL and WASO, will also be assessed. A linear mixed model will examine the post-treatment sleep values using the baseline covariates. **Aim 2:** A comparison of face-to-face versus attention control will use an analogous statistical methodology as described above for Aim 1. **Aim 3: (rumination and sleep reactivity):** Q-learning[138-140] will be used to identify baseline and time-varying factors that predict the better second-phase intervention among non-remitters to *d*CBT-I. We will also generalize and apply mediator analysis methodologies[141] for examining the mechanisms of action by which the treatment groups exhibit their effects (i.e., targets). We will examine baseline predictors (e.g., sleep reactivity, race, SES) of change in outcomes (i.e., group x condition interaction) to establish the critical need for early risk-detection and prevention for highly reactive sleepers, and demonstrate the potential for prevention in thoes with elevated risk factors (i.e., sleep reactivity, SES, race).

Assessment of reduction in suicidal behavior and related outcomes: Columbia-Suicide Severity Rating Scale (C-SSRS) will be included in all assessments. Appropriate action (ER referral, hospital admission, MH referral) will be taken as necessary, and C-SSRS data will be collected for supplementary analyses.