Sleep To Reduce Incident Depression Effectively (STRIDE)

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Research Strategy

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Depression rates have remained largely unchecked in the US due to poor detection of risk for major depressive disorder (MDD), which leads to missed opportunities for primary prevention. However, one solution may be insomnia intervention, as people with insomnia disorder are at markedly high risk for incident depression. Furthermore, insomnia is the most frequent residual symptom domain that persists despite successful treatment of MDD, and is a predictor of relapse. As insomnia is a modifiable risk factor for depression, targeted insomnia treatment may reduce incident depression. As limited availability of sleep specialists is a barrier to nonpharmacological treatment of insomnia, integration of web-based technology with primary care services offers a novel solution. Along with our preliminary data, previous 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 a novel application of this approach that is widely accessible, scalable and cost-effective for both patients and providers. The proposed intervention will leverage primary care as an entry point for early sleep intervention, as identification and treatment of both MDD and insomnia typically first occur in primary care.

We propose a large-scale clinical trial in primary care utilizing a stepped-care model to determine the *effectiveness* of *d*CBT-I alone or in combination with traditional face-to-face cognitive behavioral therapy for insomnia (CBT-I), and the effects of these established sleep interventions on the prevention of depression. This stepped care trial utilizes a "SMART" design by randomizing to internet-based *d*CBT-I or an attention-control group. Following this phase, a second randomization to face-to-face *clinician-based* CBT-I or attention control will be provided to patients who do not respond to *d*CBT-I. <u>The present trial represents an innovative combination of these insomnia therapies with potential for real-world implementation and scalability</u>. Another important and unique component of the trial is the 1-year follow-up assessment of participants to determine the durability of digitally- and traditionally-delivered behavioral insomnia treatments over time, and 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 (SOL) and wake after sleep onset (WASO) 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 or < 8 point ISI reduction), 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 using face-to-face CBT-I to treat insomnia in non-responders 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 <u>*prevention*</u> of **2a)** incident depression and **2b)** depression relapse. These aims will be tested by comparing the 1-year rate of depression outcomes of both *d*CBTI and CBT-I to an attention control group.

Aim 3a) (Exploratory) Evaluate changes in nocturnal rumination as a modifiable behavior (post-treatment) that <u>mediates</u> the effect of insomnia treatment on subsequent depression-risk.

Aim 3b) (Exploratory) Determine the <u>moderating</u> 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

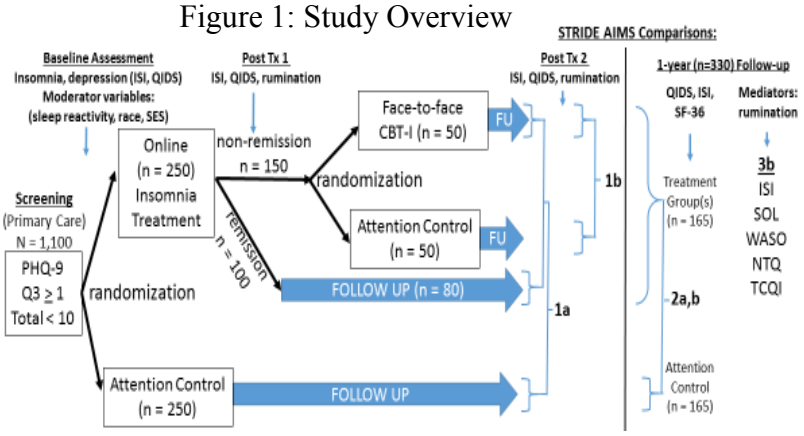
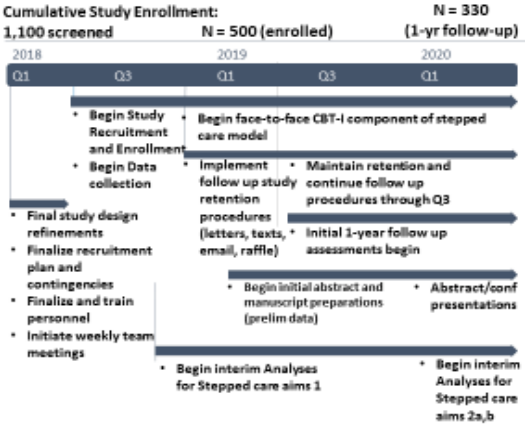


Figure 2: Study Timeline and Milestones



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We propose to enroll 500 trial participants (insomnia without depression) in alignment with ongoing data collection procedures within the HFHS network of sites in southeastern Michigan. Baseline assessment will include the utilization of standardized and validated assessment tools for insomnia and major depressive disorder.[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, at which point the T group will receive their first treatment with the utilization of Sleepio (www.sleepio.com), an online cognitive behavioral therapy for insomnia *d*(CBT-I).[83] Participants will receive 6 weekly sessions of online *d*CBT-I. Specifically, participants are immersed in a fully automated media-rich web environment, driven dynamically by baseline and progress data. 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.

Those without insomnia remission following *d*CBT-I (ISI > 10)[68] treatment (typically 40%) 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 following recommendations for effectiveness trials with 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 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. Additionally, during the initial screening, those with depression (PHQ-9 or QIDS moderate) will be excluded.

Overall, we are assuming an attrition rate of approximately 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 a stipend of $20.00 per assessment and follow up.

We will also test treatment effects on quantitative sleep parameters including ISI, sleep onset latency (SOL), wake after sleep onset (WASO), and sleep efficiency collected using standardized report-based measures. Sleep diary data will be collected as part of the standard of care during each treatment to analyze trends across time.[91] Depression outcomes will be measured by the 16-item Quick Inventory of Depressive Symptomatology (QIDS),[77] which is more extensive than the PHQ-9 and will be measured pre- and post-treatment during an online assessment following screening. As sleep is a component of the QIDS assessment, items relating to insomnia will be removed for all analyses (see below). Both study entry and case identification will include QIDS criteria for chronic nonpsychotic, major depressive disorder.[77] To enter the study participants will need to score less than an 11 on the QIDS. During year 1 follow-up, MDD cases will be identified (new onset, recurrence) for those who meet criteria of greater than or equal to 13 or a lower sub-threshold cut off greater or equal to 11 to increase sensitivity.[77,82]

TARGETS

Rumination (mediator): refers to the perseveration of negatively-valenced thoughts, which critically increases risk for depression.[93] To test the possibility that insomnia-induced rumination serves 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 to test for the possibility that rumination is a primary component in the development of depression in individuals with insomnia. The target (mediator) in the proposed studies is state-rumination, specifically, nocturnal rumination which will be assessed using the Thought Control Questionnaire Insomnia-Revised (TCQI).[98] Whereas good sleepers get an adaptive reprieve from rumination at bedtime, insomnia extends rumination into the night.[106] Further, the inability to fall asleep at night can itself trigger negative schemas, such as helplessness and lack of control, that provide additional content for rumination.[107] While good sleepers think about *'nothing in particular'*, insomniacs engage in nocturnal rumination about daytime stressors or the adverse effects of poor sleep. Insomnia may thus 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 moderate the effects of sleep improvement on depression. **Identifying a significant moderator(s) of treatment impact could lead to the development of cost-effective strategies to triage those at**

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greatest risk for depression into effective preventative programs of treatment. 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): To identify baseline and time-varying factors that predict the better second-phase intervention among non-remitters to Sleepio, Q-learning[138-140] will be used. 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 greater impact in terms of prevention for individuals 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.