Cover letter for study protocol submission

Title of Study: *Effect of yoga in chronic insomnia: A randomised controlled trial*
Sponsor / Responsible Party: All India Institute of Medical Sciences (AIIMS), New Delhi
Ethical Approval: Institutional Ethics Committee (IEC), AIIMS New Delhi – Approval granted on 27 February 2025 (Ref. No.: AIIMSA3146)
Date: 27 February 2025
Trial Phase: Interventional – Randomised Controlled Trial
To
The ClinicalTrials.gov Protocol Registration and Results System (PRS) Team
Please find enclosed the study protocol for the above-mentioned clinical trial, submitted as part of the trial registration process on ClinicalTrials.gov. This protocol has been reviewed and approved by the Institutional Ethics Committee (IEC), AIIMS New Delhi, as per the details provided above.
We request you to kindly review and include this protocol in the public trial record for transparency and compliance purposes.
Sincerely,
Dr. Nasreen Akhtar
Additional Professor
Department of Physiology
All India Institute of Medical Sciences, New Delhi
Email: drnasreenakhtar@gmail.com
Phone: 91+ 9899264164

Introduction:

Chronic insomnia (CI) is a common sleep disorder with a global prevalence of about 10%-22% and a prevalence in India of 28.1% in adults aged (30-60 years) (*Bhattacharya et al, 2013).* Chronic insomnia occurs when, despite adequate opportunity for sleep, patients complain of difficulties falling asleep, maintaining sleep, or experiencing sleep as non-restorative and of poor quality, and these problems occur at least three times per week for one month. Sleep complaints in insomnia are accompanied by disturbed daytime functioning, fatigue, and mood disturbances (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition DSM - 4TR).

An integrative model for etiology and pathophysiology of insomnia disorder includes the cognitive-behavioural domain, which defines the psychological and dysfunctional beliefs that affect sleep, and the neurocognitive and neurobiological domains, which address the neural and molecular mechanisms involved in sleep disturbances.

The neurophysiological model explains the behavioral effects associated with meditative state like reduced levels of arousal, enhanced sensory excitability, decreased autonomic arousal and shutting down of complex analytical processing, relaxation response includes heightened feeling of subjective well-being, decreased arousal, generalized decrease in decreased core body temperature, decreased adrenergic tone, reduced muscle activity as recorded by EMG and decreased respiratory rate. These effects are considered as antidotes to stress induced pathophysiological responses (Benson et al). The systems network model proposes mechanisms of stress relaxation by the practice of yoga.

The current standard of care for insomnia is cognitive behavior therapy (CBT) and pharmacotherapy (sedative, hypnotics, over the counter sleep aids) and unfortunately, sedatives and hypnotics lead to CNS toxicities, possible drug interactions with cancer therapeutics, dependency, and rebound sleep impairment after discontinuation (krystal et al 2019). CBT has been established as the first

line treatment but may not be appealing to everyone. Besides delay in therapeutic response by CBT, shortage of trained manpower, and compliance issues with patients make this an unattractive option. Lifestyle interventions, such as exercises, sleep hygiene, tai chi, sleep restriction etc provide an additional treatment option, and current guidelines for the treatment of impaired sleep recommend using them in conjunction with drugs and CBT.

Yoga is an age-old established practice in India. Yoga is a comprehensive discipline with the aim of the achievement of physical, psychological, and spiritual health and well-being. It incorporates a wide variety of postures/exercises, breathing, and meditation techniques. Some studies have shown a promising use of yoga in insomnia. But there are very few randomised controlled trials reported. The common yoga protocol consists of three groups of exercises: sustained postures, breath control, and meditation. All three combined restructure cognitive, emotional, behavioural, and autonomic domains. We propose a model for the mechanism of action of yoga in chronic insomnia based on the hyperarousal model of insomnia. There are four pathophysiologic processes, neurophysiologic hyperarousal, increased somatosensory information processing, impaired psychological and behavioral processes and activation of autonomic systems by stress mechanisms. In this study we will investigate the mechanism of action of yoga chronic insomnia.

Rigorous randomized controlled trials on the efficacy of yoga with a precisely designed and timed regimen of yoga and adequate and appropriate controls are lacking. The aim of this study is to perform a randomized controlled trial on the effect of yoga in chronic insomnia.

Methods

The aim of this study is to investigate the effect of yoga in patients of chronic insomnia. The objectives are to assess the impact of yoga on key parameters in these patients, including the Insomnia Severity Index, sleep

architecture, and dysfunctional beliefs and attitudes about sleep. Additionally, the study seeks to evaluate changes in salivary cortisol and alpha-amylase levels, as well as alterations in somatosensory information processing, following the practice of yoga

Hypotheses

The pathophysiology of Insomnia consists of neurophysiological hyperarousal, increased somatosensory processing, impaired psychological and behavioural processes and increased autonomic arousals during sleep due to activation of stress axis. Yoga is known to improve all the four processes. This may improve sleep. We hypothesize that in patients of chronic insomnia compared to standard care, additional intervention of 8 weeks of yoga will be associated with better outcomes as per insomnia severity index.

Trial design

The trial will be conducted in Dr. Baldev Singh Sleep Laboratory, Department of Physiology AIIMS New Delhi. This protocol has been approved by the Institute Ethics Committee of All India Institute of Medical Sciences, Ansari Nagar, New Delhi on 27.02.2025 (Ref. No. : AIIMSA3146).

This is a 3-arm parallel group, assessor blinded, randomised controlled trial which conforms to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The protocol is drafted in accordance with Standard Protocol Items: Recommendations for Interventional Trials. We propose to conduct a three-group parallel, assessor blinded randomised controlled trial (RCT) to test the superiority of addition of practice of yoga to standard care of chronic insomnia.

Patients will be allocated to three treatment arms. The first group will receive the Common Yoga Protocol in addition to the standard of care, which includes yoga practice along with medications, with or without Cognitive Behavioural Therapy (CBT). The second group will participate in a stretching regimen alongside the standard of care, involving sham yoga practice combined with medications, with

or without CBT. The third group will receive only the standard of care, consisting of medications with or without Cognitive Behavioural Therapy.

Permuted block randomisation will be performed. Assignment to a group will be determined by a computer-generated random allocation schedule operated by an independent researcher. Assessment will be done at three time points, at baseline, and after 2 and 8 weeks of intervention.

Participants and recruitment

Participants will be recruited from the outpatient department of psychiatry and neurology, AIIMS New Delhi and from the general community. A total of 72 eligible patients will be randomized and allocated equally into three groups: the yoga group, stretching group, and the control group. The sample size was determined based on a n expected effect size of 0.9, with a statistical power of 80% and an alpha error of 0.05. This calculation ensures adequate power to detect meaningful differences between the groups, minimizing the risk of Type I and Type II errors. Each participant will receive treatment for a total duration of eight weeks. The intervention will consist of two weeks of supervised yoga sessions, followed by six weeks of home-based yoga practice. Participants included in the study were adults from 18 to 65 years of age, of either gender, meeting the diagnostic criteria for chronic insomnia as per the (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition DSM - 4TR) (DSM-4 TR). All participants will be required to have the capacity to provide informed consent.

Exclusion criteria will comprise a current diagnosis of any other sleep disorder, including restless legs syndrome (RLS), periodic limb movement disorder (PLMD), circadian rhythm sleep-wake disorders, narcolepsy, or parasomnias. Individuals with imminent suicide risk, those engaged in shift work or who had undertaken transmeridian travel within the past two weeks, pregnant or lactating females, and those with excessive caffeine intake (equivalent to >3 cups of coffee per day) or high alcohol consumption (>2 standard drinks per day on ≥4 days per week) were excluded. In addition current substance (drug or alcohol) abuse and the presence

or recent exacerbation of any serious chronic medical condition likely to interfere with participation in the study were excluded

Randomisation and allocation concealment: The random allocation sequence was generated with a block of 6. Randomisation numbers will be sealed in a predetermined computer-made randomisation opaque envelope. The patients' screening sequence numbers will be printed outside the envelope, whereas the group names will be printed inside. All envelopes will be numbered consecutively and connected. Researchers who screen the eligible patients after baseline will separate the envelopes from the strain and open them according to the patients' screening sequence number and then assign the patients to either yoga-intervention group, stretching group or only standard of care group

Blinding: Assessor blinding will be accomplished through the coding of patient data. Although participant blinding is not feasible, an active comparator (stretching group) can help reduce expectancy bias.

INTERVENTION

Intervention group

Participants allocated to the intervention group will undergo an 8-week yoga therapy program, consisting of 2 weeks of supervised in-person sessions followed by 6 weeks of monitored self-practice. The yoga intervention will be based on the Common Yoga Protocol developed by the Ministry of AYUSH, Government of India, with time-specific modifications suitable for the study. The protocol can be accessed via the official AYUSH portal http://ayush.gov.in/booklets-common-yoga-protocol-0. During the initial supervised phase, participants will be trained by a qualified yoga instructor thoroughly experienced in delivering the Common Yoga Protocol. To ensure consistency, only one or similarly trained yoga expert will be assigned to conduct the sessions. The subsequent self-practice phase will be supported through weekly virtual follow-ups via zoom calls, conducted jointly by the investigator and the yoga instructor to monitor adherence and address

participant concerns. A comprehensive educational session will be conducted at the onset of the intervention to enhance understanding and compliance. Participants will have continuous access to the study investigator to report difficulties or seek clarification. These measures aim to optimize adherence and ensure the standardized delivery of the intervention.

Stretching group

Participants in the stretching group will practise supervised stretching protocol for continuous 2 weeks followed by 6 weeks of self-training which will be monitored through zoom calls by the researcher and yoga instructor.

Control group

Participants in the control group will receive only standard of care with no intervention. Their baseline, after 2 weeks and after 8 weeks assessment will be done.

Description of similarity of intervention: Standard care includes pharmacological intervention and/or Cognitive behavior therapy which will be similar for both groups. The intervention group will receive yoga training in addition. The control group will be kept on a wait list if they choose to join after the trial is over.

Outcome measures

Primary outcome: Severity of insomnia as assessed by Insomnia Severity Index, an increase in mean insomnia severity of the group, 8 weeks post commencement of intervention.

Secondary outcomes: Latency of persistent sleep, total sleep time, sleep efficiency and WASO based on Sleep Consensus sleep diary, actigraphy and polysomnography, microarousals including autonomic arousals during sleep based on polysomnography, perceived depression and anxiety scale, dysfunctional beliefs about sleep scale, stress biomarkers including cortisol, alpha amylase , sympathetic and parasympathetic activity as measured by

heart rate variability measures, cortical sensory processing based on quantitative sensory testing.

Baseline questionnaires including patient demographics, sleep patterns, insomnia history, sleep related lifestyle history and medical history will be filled.

Primary Outcome

Insomnia Severity Index (ISI): Insomnia Severity Index is a seven-item questionnaire designed to assess the nature, severity, and impact of insomnia. It uses a Likert-type scale where respondents rate various aspects of their sleep problems. The key components are: Difficulty falling asleep, difficulty staying asleep, problem waking up too early, satisfaction with current sleep pattern, interference with daily functioning (e.g., daytime fatigue, ability to function at work or daily chores, concentration, memory, mood), noticeability of sleep problems to others, distress caused by the sleep problem, distress caused by the sleep problem. The scores range from 0 to 4 for each item, with higher scores indicating more severe insomnia. The total score can help determine the severity of insomnia: 0-7: No clinically significant insomnia, 8-14: Subthreshold insomnia, 15-21: Clinical insomnia (moderate severity), 22-28: Clinical insomnia (severe).

Secondary outcome:

Polysomnography: Digital polysomnography (PSG) - Overnight PSG will be done using Somnomedics© PSG system with the standard montage. Electroencephalography (EEG), Electro-oculography (EOG) and Electromyography (EMG) will be sampled at 256 Hz. The low frequency and high frequency filter setting will be EEG-0.3,35 Hz; EOG-0.3,35 Hz; EMG-10,256 Hz; EEG, EOG and EMG channels will be placed along with pulse oximeter, RIP belts for thoracic and abdominal movements, Electrocardiography (ECG), oronasal pressure cannula and thermistor sensors according to American Association of Sleep Medicine (AASM) guidelines. Notch filter at 50 Hz will be put and

simultaneous video monitoring will be done with the PSG device during the entire night. The staging of the sleep will be done using AASM criteria and relative percentages of various sleep stages will be calculated. Parameters like TIB, TST, WASO, SPT, Sleep Period Time (TST+ WASO), SOL:Time from start of recording to first epoch of sleep and, REM Latency, SE = TSTx100/TBT will be calculated. Various stages of rapid eye movement sleep (REM) and NREM sleep (N1, N2, N3) will be scored and calculated as percentage of TST and TIB.Calibration will be performed both at the beginning and the end of the study as per AASM criteria. Physiological/biological calibration has to be performed as follows: ask the patient to keep the eyes open, look straight ahead for 30 s, close the eyes, look straight ahead for 30 s, look to the left and right, repeat up and down, hold head still, blink eyes slowly five times, grit teeth, clench jaw or smile, inhale and exhale, hold breath for 10 s, flex right foot, flex left foot, flex right hand, flex left hand, turn the patient to either side to check on the body position sensors.

Actigraphy and Sleep Diary : It is a method for inferring sleep/wake cycles based on magnitude of wrist movement collected using digital devices called actigraphy watches. It will be used to record the pattern of sleep for 3 continuous days before and after intervention.

Parameters which will be estimated with standard sleep logs include: sleep latency (SL), total sleep time (TST), wake after sleep onset (WASO) and sleep efficiency (SE = TST / time in bed)

Dysfunctional Beliefs and Attitudes About Sleep (DBAS): Dysfunctional beliefs and attitudes about sleep refer to unhelpful or incorrect thoughts and perceptions about sleep that can contribute to or worsen insomnia. These beliefs often involve unrealistic expectations, excessive worry about the consequences of poor sleep, and misattributions about the causes of sleep difficulties. Common dysfunctional beliefs include “I must get 8 hours of sleep every night to function well”, “If I don't sleep well tonight, I'll be a complete mess tomorrow”, “My insomnia is due to a serious medical condition”, “Taking a sleeping pill is the only way to ensure a good night's sleep”.

Epworth Sleepiness Scale (ESS): The Epworth Sleepiness Scale is a self-administered questionnaire used to measure daytime sleepiness. It consists of eight situations where you rate your likelihood of dozing off or falling asleep on a scale from 0 to 3. The situations are: Sitting and reading, Watching TV, sitting inactive in a public place, being a passenger in a car for an hour, lying down in the afternoon, sitting and talking to someone, sitting quietly after lunch (no alcohol), stopping for a few minutes in traffic while driving. The total score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness.

Depression Anxiety stress scale (DASS-21): The DASS-21 (Depression Anxiety Stress Scale-21) is a concise psychological assessment tool designed to evaluate the levels of depression, anxiety, and stress. It is 21 items total, with 7 items each for depression, anxiety, and stress. Scoring: Each item is rated from 0 to 3. Score 0 = Did not apply to me at all, 1 = Applied to me to some degree, or some of the time, 2 = Applied to me a considerable degree, or a good part of the time, 3 = Applied to me very much, or most of the time

Biomarker Estimation: To assess the level of stress, salivary cortisol and salivary alpha amylase will be estimated through ELISA. Saliva samples will be collected before intervention, at 2 weeks and after intervention as biomarkers of stress. Samples will be stored at -80˚ C for further biochemical analysis.

Somatosensory information processing: It involves assessment of somatosensory evoked responses to noxious or innocuous stimuli using controlled thermal test modalities. Stimuli are systematically applied to an anatomical test site until the study participant reports sensation or pain. The participant's responses to external stimuli can be assessed at the affected anatomical site. For thermal testing, a small probe called a thermode is attached to the patient's skin. The system is capable of heating or cooling the thermode temperature as needed. The temperature change is achieved by controlling their heat generator inside the thermode (a Peltier element) and measuring the output

temperature using thermistors. Parameters which will be assessed are: Warm detection threshold (WDT), Cold detection threshold (CDT), Hot pain threshold (HPT), Cold pain threshold (CPT), Hot pain tolerance threshold (HPTT), Cold pain tolerance threshold (CPTT).