Lavender vs Zolpidem Sleep Quality During Diagnostic Polysomnography

IRB: A19-156

NCT: 04102345

Clinical Study Protocol and Statistical Analysis Plan

Amendment 1 Date: 31 December 2019

Sponsor

HealthPartners Institute

This study will be conducted in compliance with the protocol, IND regulations and other applicable regulatory requirements.

Participant Contact Project Narrative

1. *Summary*

   A common problem associated with sleep studies (polysomnogram or PSGs) is "first night effect" (FNE), with disruption of sleep, resulting in insufficient time to make a diagnosis or achieve effective therapy [1]. Current practice is to prescribe sleep aids or sleep medications to prevent FNE. Zolpidem (Ambien) is the most commonly prescribed medication, but has several significant side effects, limiting its usefulness [2]. Hence, it is important to find an alternative that is safer, more acceptable and personable to patients. In this study we propose to prospectively evaluate sleep related outcomes with lavender aromatherapy compared to those with pre-medication prior to diagnostic or split night polysomnography (PSG).

2. *Study aims*

   Overall Objective: *To* determine if lavender aromatherapy is as effective as pre-prescribed zolpidem in improving PSG quality, and reducing the need for repeating PSGs for a diagnostic or split night sleep study.

   > ***Primary Outcome:***
   > - Sleep efficiency
   >
   > ***Secondary Outcomes:***
   > - A successful split night PSG or a diagnostic PSG and wake after sleep onset (WASO)
   >
   > ***Exploratory Outcomes:***
   > - Total sleep time (TST), sleep onset latency, REM sleep onset latency, Stage 3/4 sleep percentage, Arousal index, side effects

3. *Background, Rationale, Significance*

   FNE is well described in both normal and pathological conditions in the literature [1]. The main characteristics of the first night effect are shorter total sleep time and REM sleep time, lower sleep efficiency, longer REM sleep latency, and decreased slow wave sleep [1]. This reduced sleep quality is probably due to multiple factors: discomfort caused by electrodes, limitation of movements, and the unfamiliar environment of the sleep laboratory. To improve recordings, the sleep lab offers individualization of the environment such as controlling temperature, personal pillows and sound proofing. Despite these factors, there is a percentage of studies reported (33-46%) that result in the need to either repeat the study or have the patient return to the lab for titrating study [2,3]. This results in increased cost as well as poorer patient experience [4]. Pre-medication with non-benzodiazepines sleep aids has been shown to decrease the likelihood of FNE [2,3], however with side effects such as falls and post-study confusion, it is important to find an alternative that is safer, more acceptable and personable to patients [5].

   Aromatherapy encompasses the therapeutic use of aromatic essential oils. These are 'non-oily, highly fragrant essences extracted from plants by distillation, which evaporate readily' [6]. Essential oils are usually presented as massage oils or lotions, in herbal packets under a pillow, or in an ambient vapor machine. The mechanisms by which they are thought to function by are: olfaction, topical absorption and/or ingestion through the oral cavity [7]. Jimbo et al, proposes the action of aromatherapy begins from a smell molecule combined with a receptor particular to each specific odor [8]. The smell molecule passes along the nasal cavity and adheres to the olfactory epithelium. The stimulus is then transmitted from the olfactory bulb to the higher sensory centers in the cerebral cortex [9]

   Lavender (*Lavender angustifolia*) aromatherapy has a long history of being commonly used for promoting sleep [10-17] with almost no side effects. Specifically relevant to this study, Goel and colleagues studied the effects of lavender using PSG in young men and women in 2005. When compared to the controls, participants in the lavender arm showed improvement in slow wave sleep, % sleep time, along with gender differentiated effects on stage 2, REM sleep and wake after sleep onset latency [18]. In addition, the prospective study conducted by the neuroscience research department with residents in memory care, showed an improvement of total sleep by 42

minutes and increase in sleep efficiency by 6.31% with lavender [19] (manuscript submitted). In this study, we hypothesize that lavender will improve sleep quality and reduce the need for repeat PSGs, as effectively as zolpidem.

Aromatherapy is currently being utilized in many Regions Hospital departments with a positive patient response and experience. In addition, the study conducted by the neuroscience research evaluating aromatherapy with total joint patients at Regions hospital showed; patients that chose aromatherapy report better patient satisfaction scores in regard to the control of pain. In line with the triple aim, we think that this study will provide an opportunity to reduce total cost of care by reducing the number of failed diagnostic PSGs (**affordability**), resulting in earlier initiation of treatment (**health**), with improved patient experience (**experience**). In addition, lavender provides a better safety profile than any sedatives that are currently being used for diagnostic sleep studies.

4. *Approach*
   a. *Study design*
      We propose to do a pragmatic clinical study by recruiting patients who are scheduled for their first in center diagnostic or split night sleep study (PSG). The overall goal for this study is to show that lavender is as effective as Zolpidem (non-inferiority analysis) with regard to improvement of sleep quality and usability of diagnostic PSGs with sleep efficiency as the primary outcome.

   b. Population
      Briefly, we will use a convenience sample (non-random selection) to recruit patients (refer to pre-screen form for recruiting patients). We plan to enroll about 144 patients, 120 who were prescribed sleep medications and 24 who agree to use lavender aromatherapy. Study would be considered complete if the enrollment was 24 or more in both groups. Patients who are not prescribed any sleep medication/aids or chose not to use them, will be offered lavender aromatherapy as an alternative. The sleep aids are prescribed by the referring doctor. We will consent both patients who are prescribed/use zolpidem during their diagnostic or split/night sleep study and those that chose lavender. At the Maplewood center, there are 45-50 sleep studies scheduled per week. We estimate that there are 15-20 patients per week that are eligible for the study.

      Inclusion Criteria
      - Age >=18 years
      - In-center diagnostic or split night sleep study (PSG)

   c. Data collection process
      i. Process steps for identification of patients or records
         Refer to Figure 1. Briefly, when the patient checks in for the sleep study, the research team reviews the chart to identify if the patient is potentially eligible for the study. The pre-screen algorithm will be used. The patients can qualify for the study
         i. If the patient is prescribed zolpidem (Ambien) by the referring doctor for the sleep study or
   ii. If the patient has not been prescribed any sleep aid.
      ii. Recruitment
         Refer to Figure 1
         If the patient is eligible;
         - scenario (i), they will be offered to participate in the study as part of the zolpidem group or
         - Scenario (ii), they will be offered to participate in the study as part of the Lavender group.

In either scenarios, the patient will be consented. Consent will be collected from both groups to ensure we can use their sleep study results.
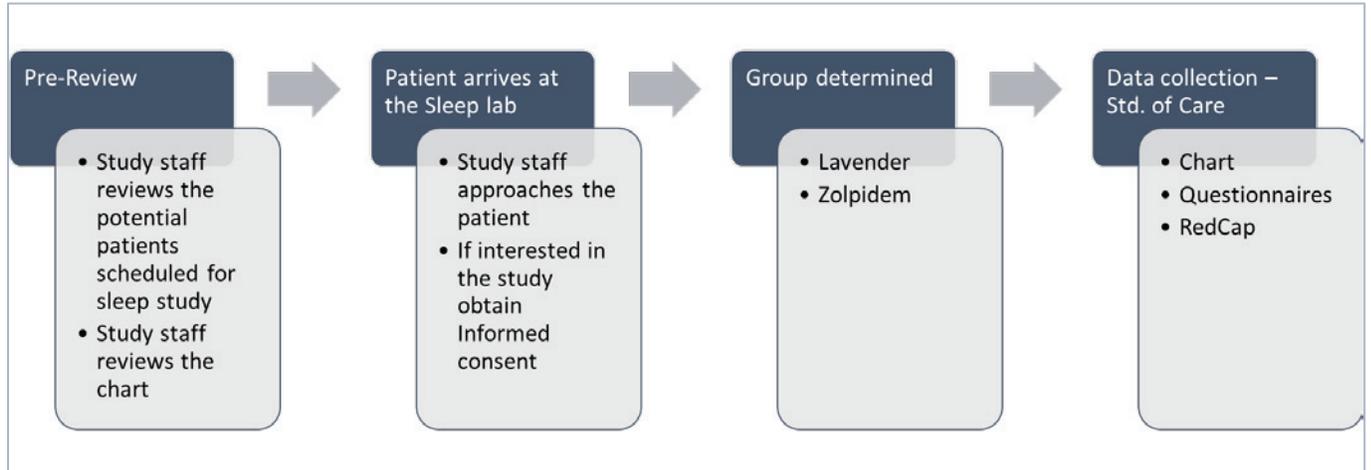
Figure 1: Process Steps

    iii.   Data sources
- EPIC – Chart review
- Questionnaires
- Polysomnogram (PSG) – Sleep Study

Refer to data dictionary for details regarding data that will be collected from each of the sources.

Table 1: Terms and Definitions – for Sleep Study

Term	Definitions
Total Recording Time (TRT)	Total amount of time during which the patient is in bed with recording equipment activated
Total Sleep Time (TST)	Total amount of sleep time scored during the total recording time; includes time from sleep onset to sleep offset and is distributed throughout the sleep time as minutes of Stage N1 sleep, Stage N2 sleep, Stage N3, and rapid eye movement (REM) sleep.
Sleep efficiency	Refers to percentage of total time in bed actually spent in sleep. It is calculated as sum of Stage N1, Stage N2, Stage N3, and REM sleep, divided by the total time in bed and multiplied by 100
Sleep Latency	Time in minutes from 'lights off' that marks the starting of total recording time to the first epoch scored as sleep
Wake after Sleep Onset (WASO)	Periods of wakefulness occurring after defined sleep onset
Apnea-Hypopnea Index	Number of apnea and hypopnea events per hour of sleep.
Total Arousals	# of transient phenomenon that may lead to wakefulness or only briefly interrupt sleep
Arousal index	Total number of arousals x 60/TST (min)
Sleep R Latency	Rapid eye movement latency is the time from the sleep onset to the first epoch of REM sleep
N1 Time	Stage N1 Sleep Time
N2 Time	Stage N2 Sleep Time
N3 Time	Stage N3 Sleep Time
REM Time	Stage REM Sleep Time
% N1	Minutes of N1 sleep stage × 100/TST

% N2	Minutes of N2 sleep stage × 100/TST
% N3	Minutes of N3 sleep stage × 100/TST
% REM	Minutes of REM sleep stage × 100/TST
Limb Movements	Repetitive limb movements that may disrupt sleep
Lights On	Time that recording of sleep is terminated
Lights Off	Time at which the patient is allowed to fall asleep and marks the start of data that will be staged and analyzed.

iv. Process steps for data acquisition
At this visit, study staff will review the consent form with the patient. All of their questions will be answered and they will be asked to demonstrate their understanding of participation. If they would like to participate, they will sign the consent form. As scheduled, the patient will undergo all the scheduled standard procedures for the diagnostic/split night study. Data will be extracted and entered into REDCap by the study staff. No data outside of standard of care will be collected.

d. Intervention, treatments
Intervention: Aromatherapy with Lavender using a diffuser. To be eligible for this intervention, the participant should not be prescribed any sleep aid. We will be using commercially available lavender essential oil and diffusers. The study staff will fill the diffuser with water sufficient to run for about two hours and recommended drops of oil will be added about 10 min before the lights are turned off. The diffusers automatically turn off (mode – two hour shut off) when the water level falls below trigger in about two hours.

Comparator: Oral Zolpidem. To be eligible for this group, the participant was prescribed zolpidem for the sleep study by referring doctor, i.e., pre-prescribed physician-directed use of zolpidem. For this group, the subjects will take the prescribed medication prior to the sleep study, as directed by the physician.

Consent will be collected from both groups to ensure we can use their sleep study results.

e. *Outcomes/endpoint and other variable definitions, and instruments used*
Sleep Efficiency: Refers to percentage of total time in bed actually spent in sleep. It is calculated as sum of Stage N1, Stage N2, Stage N3, and REM sleep, divided by the total time in bed and multiplied by 100

A successful split night PSG or a diagnostic PSG: Is a binary outcome (yes/no) based on chart review. The outcome will be inferred from documentation in the chart either in notes or PSG report showing a successful split night or if a diagnosis is made or if a repeat PSG is ordered.

Wake after sleep onset (WASO): Periods of wakefulness occurring after defined sleep onset

Side effects: For both the interventions, the side effects will be inferred from post sleep study questionnaire. The side effects will be described and compiled as a binary outcome (yes/no). This will be used to report the safety profile of the two interventions as an exploratory outcome.

Please refer to attached data dictionary for details.

f. *Statistical analysis plan*
Outcome measures will be graphed and visually assessed to determine if the planned analyses are appropriate for the distribution of the outcomes. Descriptive statistics (means, standard deviations,

frequencies, etc.) will be calculated overall and by group for the population demographic variables. We will then compare these characteristics between the two groups using t-tests, Wilcoxon, chi-square, and Fisher's exact tests, as appropriate. Missing data will be considered to be missing at random and those subjects will be excluded from analysis. If a large proportion of data is missing (>10%), we will compare baseline characteristics between subjects with missing and non-missing data. No adjustment for multiple comparisons will be done.

All statistical analyses will be performed in SAS Version 9.4. This analysis plan was written by and will be executed by Lauren Erickson.

Primary Outcomes:
Non-inferiority of sleep efficacy when using lavender versus zolpidem will be assessed using a one-sided, two-sample t-test. A noninferiority margin of 6% will be used for sleep efficiency (see power calculation for justification). The null hypothesis of inequality (difference is greater than or equal to 6%) is rejected in favor of the alternative hypothesis of equality (difference is less than margin) if the 1-sided p-value is less than 0.025. Due to the inflated probability of a type 1 error with unequal sample sizes, we will perform a sensitivity analysis in which a random sample of 24 active control participants will be compared to the lavender group.

Secondary Outcomes:
The secondary outcomes, rate of successful split night PSG and wake after sleep onset (WASO) latency will be analyzed similarly to the primary outcome. The noninferiority margins for successful split night PSG and WASO are 13.5% and 16 minutes, respectively, and are based on data from the three Lettieri studies[2,3,20].

Exploratory Outcomes:
This is a descriptive aim. All values will be summarized using means and standard deviations or frequencies and percentages, as appropriate.

g. *Power analysis or statement of precision*

We reviewed 3 previous studies by Lettieri[2,3,20] in which the pooled average sleep efficiency was 88.3% for treatment groups versus 79.0% for controls. The absolute defference in sleep efficiency was 9.3% (CI: 6% - 12.3%). We, therefore, will define the lower bound of our confidence interval, 6%, as the operative noninferiority margin.

It is estimated based on clinical experience that five times as many people have a sleep aid prescription upon arrival to the sleep clinic. This was accounted for in the power calculation. Therefore, group sizes of 24 (treatment) and 120 (control) achieve 80% power to detect non-inferirority using a one-sided two-sample t-test. The noninferiority margin is 6%, the true difference between the means is assumed to be 0, the alpha level is 2.5% and the data are assumed to be drawn from populations with standard deviations of 8.4 and 13.3.

This power calculation was conducted using the Non-Inferiority Test of the Difference of Two Means function in PASS.

h. *Strengths and limitations*
There is potential for bias due to non-randomized nature of study. We will compare baseline characteristics to determine if the groups are inherently different.

5. Setting/Environment/Organizational feasibility

This study will be conducted at the Maplewood Regions Hospital Sleep Laboratory. This location is appropriate, as the sleep studies are scheduled at this location. We think that this will not disturb the standard practice at the lab as it adds about 5 to 10 min to normal care. The staff time for research is compensated and is supported by the department leaders.

6. Risks and Benefits

There are minimal psychological or physical risks from participating in this study. The largest risk is the possibility of an allergic reaction or sensitivity to lavender. The risk of uncovering a previously unidentified allergy is low.

7. Data Confidentiality and Privacy

This study involves almost no risk. There is possibility of a confidential breach of the collected data, which may result in risk for reputation and social risk. To minimize the risk of data breach, the records of the study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify the participant. Research records will be locked up or stored on a secure server with password protection and only researchers on this study will be able to use the records.

8. Timeline

Jan – April 2018 (Study Development)
- Prepare and Submit Application to Conduct Research/IRB

May – Nov 2019
- Recruitment, Enroll Patients
- Data Collection

Dec 2019– Mar 2020
- Analyze and interpret data
- Prepare abstract and manuscript

9. Dissemination/Sharing Results/Integration and Impact

We will disseminate results through presentation at internal Sleep meetings, and medical exective committee meetings for red fund. We also plan to publish the results in conferences and peer-reviewed journal for sleep.

10. References

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