NCT03307005

Improving Sleep Quality in Heart Failure

February 27, 2018

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JHM IRB - eForm A – Protocol

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1.   **Abstract**

Heart failure (HF) affects almost 6 million people in the US, leading to significant morbidity, mortality and an impaired quality of life. Additionally, there are an estimated one million HF-related hospitalizations every year in the US, resulting in an estimated $30.7 billion in both direct and indirect costs. Despite recent advances in pharmacological and nonpharmacological HF-targeted therapies, HF-associated hospital admissions have not declined. Accordingly, consideration needs to be given to managing HF-associated comorbidities in an effort to reduce morbidity, mortality, and decreased quality of life associated with HF.

Poor sleep quality is a prevalent complaint in the HF population with an estimated 70% of HF patients chronically experiencing at least one of the following three symptoms: 1) difficulty falling asleep; 2) difficulty maintaining sleep; 3) or early morning awakenings. Several studies have demonstrated an increased prevalence of poor sleep quality in HF patients. Moreover, poor sleep quality is associated with a reduction in health-related quality of life (HRQOL) in HF patients. Poor sleep quality has several physiological sequelae including increased sympathetic activity and perturbations of the hypothalamic-pituitary-adrenal (HPA) axis. Consequently, patients with poor sleep quality may exhibit increased heart rates, reduced heart rate variability, increased blood pressure and increased risk of arrhythmias, all of which have an unfavorable effect on HF. Furthermore, with chronic stimulation of the HPA axis, there is an increased risk of development of hypertension, diabetes, and even cardiovascular disease. Eventually, the biological consequences of poor sleep can potentially compound the already stressed cardiovascular system in HF patients, leading to progression of HF and in turn, cause further deterioration in sleep quality, thereby creating a perpetual cycle.

The limited available evidence intimates that improving sleep quality in patients with HF may improve morbidity and quality of life in this patient population. However, there is a paucity of evidence assessing the use of effective pharmacologic therapies in HF. The nonbenzodiazepine, GABA receptor agonist, zolpidem, has been found to have considerable benefits over traditional benzodiazepines as a soporific medication. We hypothesize that by improving sleep architecture, zolpidem, a nonbenzodiazepine, GABA receptor agonist, will decrease the propensity for central SDB events by decreasing the frequency of arousals and preventing associated decreases in pCO_2 below the apneic threshold.

2. **Objectives** (include all primary and secondary objectives)
   a. Characterize and compare sleep parameters in heart failure with reduced ejection fraction (HFrEF) in the setting of zolpidem tartrate vs placebo. Specifically, we will compare:
      i. Sleep latency (min), Total Sleep Time (min) and Sleep Efficiency (%)
      ii. Proportion of NREM vs REM sleep (%)
   b. Determine if improvements in sleep quality correlate with improvement in sympathovagal balance
   c. Investigate whether zolpidem tartrate subjectively improves insomnia symptoms and health-related quality of life (HRQOL) in HFrEF
   d. Examine how zolpidem in heart failure patients with poor sleep quality impacts heart rate variability

3. **Background** (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The increased prevalence of poor sleep quality or insomnia in HF patients has been demonstrated in several studies. In one study of 84 HFrEF patients, 56% reported trouble sleeping and 33% of the patients reported using a sleep aid, most commonly used were benzodiazepines, followed by zolpidem. To date, there has been only one study investigating the tolerability of zolpidem in patients with HF. This study, involving 15 patients with ischemic cardiomyopathy (EF < 45%) and NYHA class I or II HF, investigated the effects of Zolpidem MR (zolpidem modified released) on sleep and nocturnal ventilation in patients with HFrEF. Participants underwent full polysomnography in a placebo-controlled, double-blind randomized trial. Zolpidem MR was well tolerated and increased total sleep time by 16% in this study. There was no change in the apnea-hypopnea index or respiratory disturbance index. We propose to expand on the very limited prevailing evidence on soporific use in the setting of HF. By prescribing zolpidem tartrate 5 mg in the proposed study (a shorter half-life form of the zolpidem at the lowest available dose), we aim to optimize patient sleep quality and minimize potential side effects. The principal investigator for the proposed study is a board-certified sleep physician who has years of experience with soporific medication use and potential adverse effects.

4. **Study Procedures**
   a. Study design, including the sequence and timing of study procedures
      (distinguish research procedures from those that are part of routine care).

The proposed study will be a randomized, parallel, placebo controlled, double blind study. We aim to enroll 50 participants. Potential subjects will be asked about sleep difficulty as outlined in the inclusion criteria. Qualifying participants will be randomized to receive either placebo or zolpidem tartrate 5 mg for a period of 7 days. Zolpidem is routinely used in a clinical setting for the treatment of insomnia. The placebo pill will be given as part of the research protocol.

Patients will complete four questionnaires including the Insomnia Severity Index (ISI) questionnaire, Pittsburgh Sleep Quality Index (PSQI), Kansas City Cardiomyopathy questionnaire (KCCQ), and the Epworth Sleepiness Scale (ESS), at the baseline visit and upon completion of the study. All four questionnaires are performed both in the clinical and research settings.

A self-applied home sleep monitor will be given to the subjects at the baseline visit after obtaining consent. The home sleep study will be repeated once between days 3-7. Home sleep studies are routinely performed in clinical practice. To reduce burden and enhance convenience, subjects will also be offered the option to have two (2) members from our study team deliver the equipment to their residence and assist in set-up.

    b. Study duration and number of study visits required of research participants.

       The duration of the study will be 8 days total. Participants will be required to complete three in-person study visits and two home sleep studies. The first in-person visit will be a baseline visit, prior to randomization, to obtain consent, describe the study, address questions, complete questionnaires, and dispense the home sleep monitor. The estimated time for this visit is approximately 60 minutes. The following day, patients will be randomly assigned to either receive zolpidem tartrate or placebo. This visit will take approximately 20 minutes. The subject will then either pick up or be mailed the home sleep monitor to repeat the home sleep study between days 3-7. The second in-person visit will be on day 8 after completion of the intervention. This visit should last approximately 45 minutes. During this visit, the subject will repeat the questionnaires.

    c. Blinding, including justification for blinding or not blinding the trial, if applicable.
       Participants and investigators will be blinded to the study drug and placebo to avoid bias.

    d. Justification of why participants will not receive routine care or will have current therapy stopped.
       Participants will receive routine care for HF with continuation of all their current therapy.

    e. Justification for inclusion of a placebo or non-treatment group.
       Placebo medication is necessary to provide a control group for comparison between the intervention (zolpidem tartrate) and no intervention without inducing bias.

    f. Definition of treatment failure or participant removal criteria.
       Participant Removal Criteria:
- Patient request
- Side effects from the intervention that are intolerable to the subject
- A significant change in clinical status such as hospitalization

    g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.
- Patients will discontinue the study drug and remain on all prior medications
- Patients can decide with their healthcare provider about treatment for sleep-related issues, including medication use.

5. Inclusion Criteria

- Age 21-79 years old
- HFrEF, EF ≤ 45% (by echocardiography)
- NYHA functional class I to III
- Able to give written consent
- On goal-directed medical therapy for HF, with stable dosing of HF medications for 2 weeks prior to enrollment
- No hospitalizations for HF within the past month
- Positive response to experiencing any of the following sleep-related symptoms at least once a week:
    - Difficulty falling asleep
    - Waking up during the night and having difficulty getting back to sleep
    - Waking up too early in the morning and being unable to get back to sleep.

Exclusion Criteria

- Use of sedative-hypnotics, anxiolytic, or benzodiazepines within the previous 2 weeks
- Current treatment with other sedating medications such as opioids
- On therapy for pharmacological therapy for depression
- History of alcohol/drug dependence
- History of liver disease, HIV, or severe COPD
- On Thorazine
- Current use of ketoconazole
- Current use of tricyclic antidepressants
- Current use of macrolide antibiotics
- Current use of anticonvulsant medications
- Pregnancy. A urine pregnancy test will be performed to exclude pregnancy in potential subjects.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.
Zolpidem tartrate is FDA approved for the treatment of insomnia. It is has a quick onset of action (typically with 30 minutes). Additionally, zolpidem's short half-life of 2.4 hours along with the fact that it does not have an active metabolite, make it relatively safe with less residual drowsiness and impairment of psychomotor and cognitive function compared to other soporific agents. Zolpidem's preferential binding to the α-1-GABA$_A$ receptor with specific sedative-hypnotic activity and less respiratory depressant effect make it a safer choice for insomnia. The minimum dose of zolpidem has been chosen (5 mg) as this the recommended dose for women and the elderly. This dose was also chosen to ensure that the minimum dose was used in the setting of HF.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.
N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.
N/A

7. Study Statistics

a. Primary outcome variable.
  Total Sleep Time (min)

b. Secondary outcome variables.
  1. Sleep Efficiency (%)
  2. Sleep latency (min)
  3. Proportion of NREM vs REM sleep (%)
  4. Change in ISI, ESS, PSQI and KCCQ between baseline and final visits

c. Statistical plan including sample size justification and interim data analysis.
  We estimate that we will need to enroll 20 participants in each arm in order to see and effect of 16% increase for the primary outcome variable of total sleep time. Thus, 25 in each arm would allow for about 20% dropout in sample. Student's unpaired t-test will be used to examine the mean difference for total sleep time between the two groups with intention to treat analysis.

d. Early stopping rules.
    N/A

8. Risks
a. Medical risks, listing all procedures, their major and minor risks and expected frequency.
  <u>Questionnaires</u>: There are no risks to completing the study questionnaires.

  <u>Overnight Home Sleep Study</u>: There are no major risks with a sleep study. Rarely, some individuals may experience minor redness or irritation at the site of the monitoring electrodes.

  <u>Zolpidem Tartrate Use</u>: The following are the most common potential risks of taking zolpidem tartrate are headache, residual drowsiness the next day, and dizziness, occurring in less than 10%. Cardiovascular risks occur in less than 1-2% and include palpitations, chest discomfort, edema, orthostatic hypertension. Sleep related activities such as sleep walking and sleep eating have been seen and occur in less than 1% of individuals.

b. Steps taken to minimize the risks.
  - The dose of zolpidem tartrate which will be used for the proposed research is the minimal dose. It is the recommended dose for females and the elderly, and the lower end of the recommended dose for males.
  - A member of the study team will place a call to each subject within 72 hours of the initiation of the medication to review any potential side effects.
  - All patients will be provided with a contact number to call with questions or concerns
  - The drug will be given only for short term use, for a total of 7 doses.

c. Plan for reporting unanticipated problems or study deviations.
  Any adverse event will be reported to the IRB by the PI.

d. Legal risks such as the risks that would be associated with breach of confidentiality.
  Breach of confidentiality would result in unauthorized individuals having access to information about the participant's medical history. Several different measures will be undertaken to protect participant confidentiality. Paper files will be in locked file cabinets. Access to any computerized information will be restricted to the study investigators or associated staff. Participant data will be stored with unique identifiers and will be password protected.

Encryption algorithms that can only be reversed with password access will be implemented. All computers will require log on passwords.

e. Financial risks to the participants.
None

9. Benefits

a. Description of the probable benefits for the participant and for society.
There are no direct benefits to subjects participating in the study. However, we hypothesize that the administration of zolpidem tartrate to patients with HF will improve sleep quality without negatively affecting respiratory status during sleep. Additionally, improvements in sleep quality in HF patients will possibly lead to a better health-related quality of life in these patients.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.
N/A

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.
Pharmacy costs to be paid by discretionary funds. Home sleep monitoring equipment is available for use from the PI and co-investigators.