Impact of Behavioral Treatment of Insomnia on Nighttime Urine Production

University of Pittsburgh STUDY19110063

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INTRODUCTION

Nocturnal polyuria (NP) has long been known to be a major contributor to nocturia in the elderly. NP has a strong bidirectional relation with poor sleep especially in the elderly; however, to the best of our knowledge, an intervention directed solely at sleep has never been tried for NP. Our previous studies have shown that improving sleep with BBTI improves nocturia. However, we do not know the mechanisms by which behavioral sleep treatments improve nocturia. The proposed study will be the first to directly examine two plausible mediators: first uninterrupted sleep period (FUSP) and NP. The knowledge gained from this study can help identify 1) impact of sleep intervention on nighttime urine production, and 2) mechanisms by which sleep intervention improves nocturia

STUDY OVERVIEW

This pilot study will provide critical preliminary data regarding the relation between sleep and nighttime urine production in seniors by: 1) examining the impact of behavioral sleep treatment (BBTI- brief behavioral treatment of insomnia) on nighttime urine production-NP and 2) exploring the potential mechanisms by which BBTI impacts nocturia. To address the proposed aims we will perform a randomized controlled pilot trial of 60 healthy community-dwelling men and women aged 65 and over with nocturia and NP. The participants will be randomized to receive the 4-week behavioral sleep intervention BBTI by a trained therapist or an information control intervention. The participants will undergo detailed sleep and bladder assessments pre- and post-intervention to assess the effect of treatment. Data from this study will provide feasibility and pilot data for a subsequent, larger, and more definitive trial.

Outcome measures:

1) Change in NP- measured by NPi- nocturnal polyuria index=(nocturnal urine volume/24-hour volume)*100
2) Change in nocturia frequency
3) Change in FUSP or duration of uninterrupted sleep before the first awakening to void

STUDY FLOW /STUDY PROTOCOL

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Screening

Screening procedures include: a) telephone interview and b) Visit 1 to study research suite - Continence Research Unit at UPMC Montefore Hospital. If the subject is interested and qualifies, then the other visits are scheduled.

Telephone Interview

Use IRB approved telephone script to determine eligibility (5-20mins; study nurse/coordinator)

ApneaLink mailed to participants who screened eligible upon telephone interview

Visit 1

2 hour; study nurse; in-person

1. Obtain informed consent and sign document.
2. Questionnaires:
    - Medical and Surgical history
    - Current medication
    - Current incontinence
    - ISI
    - MoCA (paper)
3. Uroflow and dip (at appropriate bladder fullness)
4. Measure flow rate and volume of normal void
5. Post-void residual measurement by ultrasound
6. Physical examination: Short physical examination.
7. Sleep/ bladder diary: Explain 3 day sleep and voiding diary instructions.
8. Zmachine: watch instruction video. The device to be worn on the 3rd night of voiding diary
9. Schedule visit 2 with enough time to complete diary.

Visit 2

Randomization

1. Follow study procedure according to the group randomized to.

Telephone follow-up

Week 2 after the visit 2- both groups (BBTI and Control)

Week 4 after the visit 2- both groups

Visit 3

For participants randomized to BBTI group

Post intervention

4 weeks post visit 2

1. Sleep/ Bladder diary (send in mail)
2. Zmachine (send in mail)
3. ISI- completed telephonically.

Inclusion/exclusion criteria

For this study researchers shall enroll: ambulatory and functionally-independent community-dwelling men and women
aged 65+ years, with nocturia ≥2/night.

Exclusion criteria:

- Unstable or acute medical or central nervous system conditions
- Untreated, current, severe psychiatric condition
- Untreated, current, severe overactive bladder syndrome
- Post void residual > 30ml
- Sleep apnea with AHI≥15
- Currently diagnosed and/or treated Obstructive Sleep Apnea, Restless Legs Syndrome, parasomnia
- CHF, by exam or NT-proB natriuretic peptide (NT-proBNP)> 30 pmol/L56
- Chronic kidney disease, stage III-V (eGFR<60)
- >14 alcohol drinks per week
- >3 caffeinated drinks (~300mg) per day

Statistical Analysis Plan

Randomization: After all baseline assessments are complete, researchers will randomize the participants in to the intervention groups in a 1:1 ratio, with random block sizes chosen from small even numbers, stratified by severity of baseline nocturia (≤3 or >3/night . To prevent educated guessing, the study statistician will reveal exact details of blocking strategy only at study completion.

Data Analysis: In addition to statistical significance, researchers will employ descriptive statistics and graphical techniques to draw conclusions. Specifically, as appropriate for a pilot study, researchers will focus interpretations on magnitudes of effects from standard statistical methods rather than their p-values, and apply graphical techniques such as needle plots to represent data at the individual level rather than based on averages. Researchers will use SAS® version 9.3 (SAS Institute, Inc., Cary, North Carolina) software, intention-to-treat philosophy, and multiple imputation for missing data in all inferential analyses.

First, researchers will compare baseline characteristics between the group using independent samples t-, Wilcoxon rank sum, chi-square and Fisher's exact tests, as appropriate. Any significant differences will be used as additional covariates in sensitivity analyses. Second, researchers will fit a series of analysis of covariance (ANCOVA) models with pre- to post-intervention change in each outcome as the dependent variable, intervention group as the independent factor of interest, and baseline value of outcome as a covariate. Magnitude and significance of intervention group term will serve as evidence for Aim 1 efficacy hypotheses. Third, for Aim 2, researchers will begin by exploring correlations of pre- to post-intervention changes in nocturia with those in FUSP and NPI. In keeping with Baron and Kenny's framework for mediation analysis, researchers will add FUSP change and NPI change (both individually and together) as additional independent variables to the Aim 1 ANOVA models. Any subsequent reduction in intervention effect will be interpreted as supporting the Aim 2 mediation hypotheses. Statistical significance of the extent of mediation will be obtained using %SOBEL, %INDIRECT and %MEDIATE SAS® macros, as appropriate.