DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER, STUDY OF ARMODAFINIL TREATMENT OF DAYTIME SLEEPINESS ASSOCIATED WITH TREATED NOCTURIA

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Institution Where Work Was Performed: Duke University
Financial support: Financial support for this study was provided by Teva Pharmaceuticals
Off-Label/Investigational Use: Armodafinil for the treatment of excessive daytime sleepiness in patients with nocturia
Clinical Trial Registration: Clinical Trial Name: A Double-Blind, Placebo-Controlled, Cross-over Study of Armodafinil Treatment of Daytime Sleepiness Associated With Treated Nocturia; ClinicalTrials.gov Identifier: NCT02151253; URL: https://clinicaltrials.gov/ct2/show/NCT02151253?term=nocturia&rank=16
Disclosures:
Xavier Preud'homme: No disclosures
Andrew Krystal:
Grants/research support: NIH, Teva, Sunovion, Neosync, Brainsway, Johnson and Johnson, Jazz, Novartis, Azevan, Eisai.
Consultant: Attentiv, BioExcel, Jazz, Merck, Neurocrine, Otsuka, Pfizer, Lundbeck, Sunovion, Paladin, Pernix,
Total Number of Figures: 0
Total Number of Tables: 2

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ABSTRACT

Study Objectives:

Nocturia, voids which disturb sleep, is the most common cause of awakenings and is associated with daytime sleepiness. Because the standard treatments for the most common causes of nocturia are relatively ineffective, many treated patients with nocturia are left with residual sleepiness. We carried out this pilot study to evaluate the potential of Armodafinil to be an effective means of addressing the sleepiness that persists in many nocturia patients despite their receiving standard therapy.

Methods:

This was a double-blind, placebo-controlled, cross-over study carried out in 28 patients with nocturia who were receiving standard clinical therapy for their nocturia and who had an Epworth Sleepiness Scale Score (ESS) of at least 10. Subjects received 4 weeks of both armodafinil (150-250 mg) and placebo with order randomized.

Results:

Armodafinil led to statistically significant improvement in sleepiness compared with placebo as indicated by the ESS (the primary outcome) ($p<0.002$) as well as the Clinical Global Impression of Improvement in Sleepiness scale (key secondary outcome) ($p=0.01$). Armodafinil did not increase nocturic events or significantly increase adverse effects vs placebo.

Conclusions:

This pilot study, the first double-blind, placebo-controlled trial assessing whether a wake-promoting therapy can improve residual daytime sleepiness in patients with treated nocturia, indicates the promise of armodafinil for addressing this residual sleepiness and provides impetus to carry out a large-scale study to definitively evaluate whether armodafinil is an effective therapy for the many patients with nocturia who experience daytime sleepiness that persists despite their receiving standard therapy for this condition.

Keywords: Nocturia, Excessive Daytime Sleepiness, Armodafinil

Statement of Significance:

Among the types of excessive daytime sleepiness, sleepiness due to nocturia has received remarkably little attention. Despite nocturia being a prevalent condition, particularly in older adults, and the ineffectiveness of standard treatments for nocturia, there has not been a single study of a therapy for nocturia-associated sleepiness. This study represents the first such trial and it provides evidence that a therapy, armodafanil, can significantly improve nocturia-related sleepiness. It is hoped that this study will lead to a much-needed increase in systematic research on nocturia and its sleep/wake effects and motivate carrying out larger trials of treatments for nocturia-related sleepiness.

I. INTRODUCTION

Nocturia, defined as voids which disturb sleep is an extremely common condition.[1] It has a prevalence of 10% among younger adults and 35-45% in those over age 60.[2-4]

Nocturia, is also the most common cause of nocturnal awakenings across all age groups.[5-7] In a U.S. epidemiologic study of those over 18 years of age, 75% indicated that nocturia was the most common cause of nocturnal awakenings.[5] In another study, more than half of adults aged 55-84 surveyed reported that nocturia disturbed their sleep on a regular basis.[6] An epidemiologic study in Denmark also identified nocturia as the most frequent cause of sleep disturbance and noted that greater nocturia frequency is associated with more severe sleep disturbance.[7] That the sleep disturbance due to nocturia is associated with sleep deprivation is suggested by evidence that nocturia is an independent predictor of sleepiness and regular napping in older adults.[8]

We also found an association between nocturia and an increase in napping in a pilot study carried out in 10 patients with 2 or more nocturia episodes per night who we compared with 5

similarly-aged healthy controls.[9-10] In that study, nocturia patients had significantly greater number of minutes napped per week than the healthy controls ($p<0.03$) and there was a trend for a greater number of naps per week in the nocturia patients ($p<0.09$).

Two of the most important causes of nocturia are: overactive bladder syndrome (OAB), a 24-hour problem of restricted bladder capacity and nocturnal polyuria (NP) a disorder of excessive nighttime urine production which increases with aging and is associated with a series of cardiovascular and renal disorders.[11-12] Although treatments exist for OAB and NP, the available data suggest that they are relatively ineffective at alleviating the nocturia. For OAB patients, anti-cholinergic medication is U.S. FDA approved for the management of this condition and is the standard first-line therapy for OAB in clinical practice. However, the available data suggest that anticholinergic medication has limited capacity to alleviate the nocturia in OAB patients.[13-17] Similarly, desmopressin, U.S. FDA approved for enuresis but not NP, is sometimes used to treat NP, however, the placebo-controlled trials of this therapy indicate that it has a modest degree of efficacy and that many NP patients treated with this therapy continue to have clinically significant nocturia.[18-19] As a result of the limited efficacy of the first-line therapies for NP and OAB, the majority of patients receiving standard-of-care treatment for nocturia in clinical practice continue to experience clinically-significant nocturia and the associated daytime sleepiness, and, consequently, suffer from impairment in function and quality of life, as well as exposure to sleepiness-associated risks. Preliminary evidence that continued nocturia is likely to be associated with daytime sleepiness is provided by a post-hoc analysis of data from a trial of desmopressin treatment for nocturia where it was found that improvement in nocturia, as indicated by a lengthening of the self-reported first uninterrupted sleep period, is associated with improvement in daytime impairment based on the Pittsburgh Sleep Quality Index daytime dysfunction subscale (sum of items related to ability to stay awake and ability to keep up enthusiasm to get things done).[20]

The objective of the current study was to carry out a pilot study which would be the first double-blind, prospective, placebo-controlled trial of wake-promoting therapy as a means of improving residual daytime sleepiness in patients with treated nocturia. It was intended that this study would demonstrate the potential of Armodafinil as an effective means of addressing the sleepiness that persists in many nocturia patients despite their receiving standard therapy.

II. METHODS

The study was approved by and performed in accordance with the policies and standards of the Institutional Review Board of Duke University School of Medicine.

II.a. Study Population:

Participants were from 18 to 90 years of age who were receiving standard-of-care clinical therapy for nocturia but continued to have excessive sleepiness (Epworth Sleepiness Scale [ESS] Score ≥ 10) and a mean of at least 2 nocturia events per night based on a combined sleep/bladder diary.[1,21,22] The ESS is a well-validated, reliable, self-report scale of daytime sleepiness in which subjects rate their likelihood of falling asleep or dozing in 8 different situations.[21-23] Additional inclusion criteria were that subjects had to be receiving standard-of-care therapy for nocturia, and had to meet standard diagnostic criteria for either OAB, NP or both prior to the initiation of current therapy based on a study physician assessment. The criteria for OAB employed was that there was: a mean number of voids at least 8 per 24 hours; mean of at least 1 void with urgency rating of at least 3 per 24 hours; and mean number of nocturia episodes at least 2 per night, where nocturia is defined as a void preceded and followed by sleep.[1,24,25] The criteria for NP employed was that 3-day bladder and sleep diary data indicated that nocturnal urine production had to account for at least 33% of total 24-hour urine production.[26] Subjects also had to have a study physician rated Clinical Global Impression of Sleepiness Scale of at least Moderate severity sleepiness where the Clinical Global

Impression Scale (CGI) consisted of a 7 point likert rating scale where the anchors were 1=”normal”; 2=”borderline sleepiness”; 3=”mild sleepiness”; 4=”moderate sleepiness”; 5=”marked sleepiness”; 6=”severe sleepiness”; and 7=”among the most extremely sleepy individuals”.[27] Subjects were excluded if they: were taking medications affecting urinary or sleep-wake function other than therapy for OAB and/or NP within 5 half-lives of baseline assessment; had a sleep disorder other than nocturia based on history and screening assessment; had an unstable medical or psychiatry condition; had a medical or psychiatric conditions affecting sleep/wake or urologic function; had a apnea-Hypopnea Index (AHI) ≥ 15 on screening polysomnogram; had periodic Leg Movement Arousal Index (PLMAI) ≥ 15 on screening polysomnogram; had a history of substance abuse or dependence in the last year; regularly consumed over 800 mg of caffeine; worked shift-work in the 3 months prior to or during the study.

Subjects were recruited through physician referral, flyer, magazine and newspaper advertisements.

II.c. Study Design:

This was a double-blind placebo-controlled cross-over trial. All subjects received 4 weeks of double-blind treatment with both placebo and armodafinil 50-250 mg with order randomized.

II.d. Study Procedures:

Prospective participants were first screened briefly by phone to assess their likely eligibility. Those who appeared to meet basic study criteria underwent a screening visit in the clinic where they were first provided with a full description of the study, asked to read and sign the consent form, and underwent a qualifying interview. In those subjects who continued to qualify the following were completed: medical and psychiatric history/physical exam, ESS, CGI, Urinalysis,

automated blood count with differential, serum chemistries, urine drug screen, pro brain natriuretic peptide and EKG. Subjects also had an assessment by a study physician (X.A.P.) with experience managing nocturia in clinical and research settings. This physician determined if the current treatment regimen represented standard therapy for the patients nocturia problem. Those not on standard therapy were referred for clinical management. The study physician also reviewed available records and carried out a careful history to determine if the subject was likely to meet diary-based criteria for NP or OAB currently or would have likely met these criteria for NP or OAB prior to initiation of current therapy.

Subjects continuing to qualify at the end of the screening visit were asked to complete a 3 day combined bladder and sleep diary at home unless they had completed such a diary in the 6 weeks prior to enrollment and there had been no changes in medications or new medical problems since the diary was completed. Diary data collection included quantitative determination of all void volumes through use of graduated specimen collection pans which were provided to all subjects. Subjects returned 4-7 days later during which their diary data was reviewed to determine if they met inclusion/exclusion criteria. Those who continued to qualify were scheduled for an in-laboratory polysomnogram within the subsequent 7 days to rule out obstructive sleep apnea or periodic movements of sleep .

Subjects continuing to qualify for the study based on the polysomnogram findings were randomized to receive 1 month of therapy with either Armodafinil or placebo (order randomized) with f/u appointments at 1 week, 2 weeks, and 4 weeks. At these follow-up appointments subjects are asked about any side effects, new medications, or changes to their medical history. After each change in medication dosage (see below) subjects received a mid-week call to assess any new issues or concerns. Subjects then underwent a two week single-blind placebo washout after the 1 month of double-blind therapy. This was followed by a second 4 week

double-blind treatment phase where subjects received the treatment they did not receive in the first month of double-blind therapy with f/u visits at 1 week, 2 weeks, and 4 weeks

At the end of the second 4 weeks of double-blind therapy subject participation in the study ended.

II.e. Study Drug Treatment Regimen:

During double-blind treatment subjects took armodafinil or placebo once daily, before 8 am. Armodafinil was initiated at a dose of 50 mg (1 tablet) and titrated to 150 mg after 1 week on the basis of the investigator's and patient's perception of efficacy and side-effects. After two weeks the medication could be increased to 250 mg or reduced back to 50 mg based on the investigator's and patient's perception of efficacy/side-effects. No increases in dosage were allowed after week 2. The dosage was decreased at a week 3 phone call if indicated on the basis of side-effects.

II.f. Statistical Analysis

The primary outcome variable for this study was the Armodafinil vs Placebo change in Epworth Sleepiness Scale (ESS) Score at the end of 4 weeks of double blind treatment. Analysis of the primary outcome consisted of repeated measures analysis of covariance where the repeated measure was treatment (armodafinil vs placebo), order of treatment (armodafinil vs placebo) was a between subjects factor, and covariates included in analysis were the number of nocturias and minutes napped.

Secondary outcome variables consisted of the Drug vs Placebo change in: the clinician-rated Clinical Global Impression of Change in the severity of sleepiness (7 point Likert Scale where

the anchors were 1=Very much improved; 2=Much improved; 3=Minimally improved; 4=No change; 5=Minimally worse; 6=Much worse; and 7=Very much worse;[27] the mean number of naps per week and minutes napped per week based on the sleep diary. Secondary analyses consisted of repeated measures analyses of covariance as carried out for the primary analysis except that the analysis of naps did not control for minutes napped.

Safety was assessed via tabulation of adverse events and in terms of the mean number of nocturias per night based on the 3-day bladder diary to assess for whether armodafinil treatment might worsen nocturia.

III. RESULTS

Eighty-one individuals signed consent and were screened for entry into this study. Thirty of these subjects met the inclusion/exclusion criteria for this study and were enrolled. Of those who were not included the reasons for this were: 1) Sleep apnea found on their screening PSG (47%); 2) Decided to withdraw during or after screening (23%); 3) Failed to have sufficient nocturia severity to qualify (15%); 4) Lost to follow-up (did not return after their screening visit and could not be reached) (9%); 4) Periodic Leg Movements of Sleep exceeded the cutoff for inclusion on the screening PSG (4%); 5) Found to meet narcolepsy diagnostic criteria during screening evaluation (2%). Of the 30 subjects who were enrolled one subject withdrew consent before taking study drug. Another subject was withdrawn prior to treatment with study drug because new information became available indicating that they did not meet study entry criteria. A total of 28 subjects were randomized to treatment and all 28 completed the study and comprised the data set with which analyses were carried out. The mean age of the subjects was 54.5 years (standard deviation = 14.2). The subjects were comprised of 7 men and 21 women and included 17 African American subjects, 9 caucasian subjects, 1 asian subject, and 1

mixed race subject. The baseline ESS score, CGI score, mean number of naps/day, mean number of minutes napped/day, and mean number of nocturic events/night appear in Table 1.

Primary Outcome Analysis

Repeated measures analysis of covariance indicated that armodafinil statistically significantly improved sleepiness compared with placebo based on the Epworth Sleepiness Scale ($F=10.5$; $p<0.004$) (See Table 1).

Secondary Outcome Analysis

Analysis of Clinical Global Impression of Improvement in Sleepiness (CGI-I) indicated that armodafinil led to significantly greater improvement in sleepiness than placebo ($F=7.8$; $p=0.01$) (See Table 1). No significant differences were found between armodafinil and placebo on mean number of naps/day and mean minutes napped/day (See Table 1).

Safety Assessments:

Nocturia Severity. There was no evidence that Armodafinil increased nocturic events. The mean number of nocturic events per night was numerically lower during the Armodafinil treatment phase compared with the placebo phase, though this effect was not clinically significant (See Table 2).

Adverse Events. The adverse events were comparable in the armodafinil and placebo treatment phases (armodafinil=11; placebo=10) (See Table 2). No serious adverse events events occurred during the study.

IV. DISCUSSION

This pilot study is the first double-blind, placebo-controlled trial assessing whether a wake-promoting therapy can improve residual daytime sleepiness in patients with treated nocturia. The results indicate that armodafinil has a statistically significant therapeutic effect on residual daytime sleepiness in treated nocturia patients compared with placebo. This effect was evident

on the Epworth Sleepiness Scale (ESS), the apriori primary outcome measure of the study, and corroborated by the findings with the Clinical Global Impression of Improvement in Sleepiness (CGI-I) the key secondary therapeutic effect outcome. Further evidence for clinical utility is that this therapeutic effect was accompanied by a favorable side-effect profile. There was no evidence that armodafinil increased nocturic events or was associated with more nocturic events than placebo. However, it should be noted that optimal clinical practice dictates that if standard-of-care treatment fails to alleviate symptoms of nocturia this should trigger a careful revisiting of the diagnosis and attempts to identify more effective nocturia therapies. The results of this study suggest that armodafinil may be considered for improving daytime sleepiness that persist while these steps are pursued.

In order to contextualize the size of the therapeutic effect found in this study, we compared this effect with the size of the armodafinil vs placebo treatment effect reported for studies of sleepiness occurring with conditions other than nocturia. The drug vs placebo effect size found in our study was 0.21 where effect size was estimated using the Cohen's D statistic.[28] This is smaller than the armodafinil vs placebo effect size (Cohen's D) observed in the treatment of excessive sleepiness associated with narcolepsy, which was 0.8 and sleepiness associated with obstructive sleep apnea (0.33-0.9).[29-33] However, it is a bit larger than the effect observed in the treatment of sleepiness associated with traumatic brain injury where an effect size of 0.16 was reported and much larger than the effect size observed with the treatment of sleepiness in cancer survivors (Cohen's D=0.07).[34-35]

The main limitation of this study is that it included only 28 subjects who had residual sleepiness despite receiving therapy for nocturia. However, the promising findings speak for the need to carry out larger studies aimed at definitively evaluating whether armodafinil is an effective therapy for the many patients with nocturia who experience daytime sleepiness that persists despite their receiving standard therapy for this condition. Additional limitations include: uncertainty as to the extent to which the results are dependent on the particular age

distribution of subjects in this study; that we did not collect and include in analysis the specific standard-of-care treatment each subject received; and that we did not obtain data on subject satisfaction with treatment and whether they would want to continue therapy with the two treatments they received.

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Table 1. Key Outcome Measures

Variable	Mean Baseline (S.D.)	Mean Armodafinil (S.D.)	Mean Placebo (S.D.)
ESS**	14.0 (3.3)	9.03 (5.18)	9.73 (4.43)
Clinical Global Impression of Improvement in Sleepiness (CGI-I)**	N/A	2.58 (1.03)	3.12 (0.82)
Mean Number of Naps/Day	0.45 (0.59)	0.48 (0.71)	0.73 (1.20)
Mean Minutes Napped/Day	31.7 (40.4)	38.9 (65.1)	40.0 (61.3)
Mean Number of Nocturic Events	2.3 (0.5)	1.6 (1.1)	1.89 (1.1)

***p≤0.05 for Armodafinil vs Placebo Difference; **p≤0.01 for Armodafinil vs Placebo Difference**

Table 2. Adverse Events

Adverse Event	Armodafinil	Placebo
Upper Respiratory Infection	4	4
Sinus Infection	1	0
Anxiety/Jitteriness	4	3
Insomnia	1	0
Nausea	1	1
Dizziness	0	1
Urinary Tract Infection	0	1
Rash	0	1