Mirabegron improves sleep measures, nocturia, and lower urinary tract symptoms in those with urinary symptoms associated with disordered sleep

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Introduction: *The role of organized sleep in overall health and quality-of-life (QoL) is critical. Nocturia necessarily disrupts the normal sleep cycle and negatively impacts one's health, work productivity, and QoL. We investigated, for the first time in an exploratory pilot, the effectiveness of mirabegron for improving sleep disturbance and nocturia.*

Materials and methods: *This was a prospective, open-label 12-week trial evaluating the efficacy of mirabegron in 34 men and women with disordered sleep and lower urinary tract symptoms (LUTS). Subjects received mirabegron 25 mg daily for 4 weeks, then increased to 50 mg. Subjects completed the Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form (PROMIS-SDSF), Jenkins Sleep Scale (JSS), International Prostate Symptom Score (IPSS), voiding diaries, and QoL questionnaires.*

Results: *PROMIS-SDSF scores decreased from 26.5 points to 19.3, representing a categorical improvement from clinically "mild" to "none to slight" sleep disturbance ($p < 0.001$). JSS scores also decreased from 14.1 to 8.3 ($p < 0.001$). IPSS decreased from 21.0 to 12.4, denoting a categorical improvement from "severe" to "moderate" LUTS ($p < 0.001$). Voiding diaries revealed 1.9 fewer voids per day ($p < 0.01$) and 0.8 fewer nighttime voids ($p < 0.05$). QoL improved from 0% in subjects who selected "mostly satisfied," "pleased," or "delighted" to 29.6% at follow up.*

Conclusions: *Mirabegron use improves nocturia and produces rapid, durable, and clinically significant improvement in sleep disturbance and LUTS in males and females with urinary symptoms associated with disordered sleep.*

Key Words: mirabegron, disordered sleep, nocturia, lower urinary tract symptoms

Introduction

Lower urinary tract symptoms (LUTS) including nocturia have an adverse impact on health-related quality-of-life (QoL), daily functioning, and work productivity.[1] There are many non-prostatic causes and risk factors for LUTS, such as sleep disorders, malfunctioning bladder detrusor, obesity, and genetic predisposition. Our previous work has demonstrated links between LUTS, obesity, and sleep disorders.[2-5]

LUTS interaction with disordered sleep is an underexplored topic. It is not surprising that nocturia has been associated with sleep disturbances, day-time fatigue, and a lower general well-being.[2] While it has previously been assumed that nocturia is the causal symptom for this sleep disturbance, we recently reported that other storage and voiding symptoms are also independent predictors associated with disordered sleep,

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TABLE 1. **Inclusion and exclusion criteria**

Inclusion criteria

1. Age ≥ 18 years.
2. Subject is willing and able to complete the micturition diary and sleep questionnaires correctly.
3. Symptoms of urinary frequency and urgency with or without urgency incontinence for at least 3 months, with an IPSS ≥ 12.
4. Moderate sleep disturbance with a mean score on the Jenkins Scale > 7.
5. Micturitions/24 hrs ≥ 8; total excretory volume of < 3L.

Exclusion criteria

1. Subject is using prohibited medications that cannot be stopped safely at the screening visit. Subject is excluded if using restricted medications not meeting protocol-specified criteria:
   (i) 5-alpha reductase inhibitor within 3 months.
   (ii) Phytotherapy for BPH within 1 month.
   (iii) Alpha blocker within 2 weeks.
   (iv) Taken an oral alpha agonist, tricyclic antidepressants, and anticholinergic or cholinergic medication within 2 weeks of the first screening visit with the following exception: topical anticholinergic eye drops used for glaucoma or inhaled anti-cholinergic used for COPD.
   (v) Taken an estrogen, androgen, or any drug producing androgen suppression, or anabolic steroids within 3 months.
2. Post void residual volume > 350 mL.
3. Female subject is breastfeeding, pregnant, intends to become pregnant during the study, or of childbearing potential is sexually active and not practicing a highly reliable method of birth control.
4. Subject has neurogenic bladder.
5. Any prior invasive intervention for LUTS (including bladder paralytics such as botulinum toxin)
6. Subject has significant stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor as determined by the investigator (for female subjects confirmed by a cough provocation test).
7. Subject has an indwelling catheter or practices intermittent self-catheterization.
8. Known primary neurologic conditions such as multiple sclerosis, Parkinson's disease, diabetic neuropathy or any neurological diseases known to affect bladder function.
9. Subject has evidence of a symptomatic urinary tract infection, chronic inflammation such as interstitial cystitis, bladder stones, previous pelvic radiation therapy or previous or current malignant disease of the pelvic organs.
10. Two documented independent urinary tract infections of any type in the past year.
11. Patient with a diagnosed sleep disorder (i.e., Obstructive Sleep Apnea) undergoing evaluation and treatment requiring change in care within 30 days of screening visit.
12. Subject has moderate to severe hepatic impairment [ALT (SGPT) or AST (SGOT) value greater than 3 times the upper limit of normal in the clinical center lab; confirmed on a second measurement].
13. Subject has severe renal impairment or end stage renal disease (i.e., creatinine greater than 2.0 mg/dl).
14. PSA level greater than 10 ng/mL at the first screening visit (if male).
15. Subject has severe uncontrolled hypertension as defined by a systolic pressure ≥ 180 mmHg and/or diastolic pressure ≥ 120 mmHg.
16. Subject has a clinically significant abnormal ECG or has a known history of QT prolongation or currently taking medication known to prolong the QT interval.
17. Subject has a known or suspected hypersensitivity to mirabegron or any of the inactive ingredients.
18. Subject has a concurrent malignancy or history of cancer (except noninvasive skin cancer) within the last 5 years prior to screening. Men with a history of prostate cancer regardless of curability are not eligible.
19. Subject has been treated with an experimental device within 30 days or received an experimental agent within the longer of 30 days or five half-lives.
20. Unable to follow protocol directions due to organic brain or psychiatric disease. History of alcoholism or any other substance abuse, which, in the opinion of the investigator, would affect compliance with the protocol.

suggesting a shared pathophysiology.[4] This association between sleep disorders and LUTS was evident in both cross-sectional studies and longitudinal RCTs.[4,5]

Mirabegron has been approved for the treatment of overactive bladder symptoms. Although mirabegron has been demonstrated to improve the storage components of LUTS,[6] whether doing so can impact sleep quality and nocturia is unexplored and serves as the basis of this investigation. Herein we propose, for the first time in an exploratory pilot, to analyze the effectiveness of mirabegron for the improvement of sleep disturbance and nocturia in LUTS patients.

We chose to evaluate the impact of mirabegron using two different sleep scores. Our primary sleep outcome measure was the Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form[7] (PROMIS-SDSF), which includes additional questions spanning a larger breadth of sleep domains and has been validated as the most accurate sleep measure in adults. We used the well-described Jenkins Sleep Scale[8] (JSS) as our secondary sleep outcome measure in order to qualify our PROMIS-SDSF findings.

Materials and methods

Trial designs and participants

This study was designed as a prospective, open-label 12-week trial evaluating the efficacy of mirabegron in 34 men and women with disordered sleep and LUTS. With IRB approval, patients were identified and recruited through the SIU Urology clinics during a 24-month enrollment period (July 2015-December 2017) using the inclusion and exclusion criteria noted in Table 1. There were two patients with sleep apnea, neither of whom was undergoing evaluation or treatment requiring change in care during the trial course.

Subjects completed the IPSS, PROMIS-SDSF, JSS, and a 24-hour voiding diary for 1-3 days after consent and for 1-3 days within a week of visits 2 through 4. After successful screening, subjects received mirabegron 25 mg daily for 4 weeks, then increased to 50 mg daily for the remainder of the study. Those not tolerating the 50 mg dose were returned to the 25 mg level. Subjects completed the study assessments at weeks 4, 8, and 12 (end of study) consisting of sleep scales (PROMIS and Jenkins), a 24-hour voiding diary for 1-3 days, QoL questionnaires, and IPSS. If the patient withdrew early from the study, an early withdrawal visit was conducted. Adverse events (AE) were reviewed by the principal investigator. Use of prescription, over-the-counter and supplemental medications were captured using self-report and recording of medication labels by the study team, Table 2.

Sleep measures

Sleep disturbance was assessed with both the 8-item PROMIS-SDSF, Table 3a, and the 4-item JSS, Table 3b. Subjects completing the PROMIS-SDSF obtain a raw score that is then converted a T-score.[9] Sleep disturbance severity is rated as follows for the corresponding T-score: "None to slight" (T-score less than 55), "Mild" (55.0-59.9), "Moderate" (60-69.9), and "Severe" (70 and over).

Conversely, sleep disturbances are considered when scoring 4 or more on the JSS.[10]

Statistical analysis

Due to the exploratory nature of the efficacy endpoints, we conducted this study as a pilot. Descriptive summary statistics were used primarily in the exploratory efficacy analysis. Subjects' age, height, weight, and other continuous baseline variables were summarized using descriptive statistics, while gender, race and other categorical variables were provided using frequency tabulations. Medical history data was summarized using frequency tabulations by organ system class and preferred term. Baseline continuous variables were compared between males and females with t-tests (or non-parametric equivalent). A mixed-model repeated

TABLE 2. **Over-the-counter and supplemental medications**

Included within the definition of sleep medications:

1. Medications within the sedative hypnotic class that are used to induce sleep.
2. All benzodiazepines.
3. Related hypnotics: Zolpidem, Zaleplon, Eszopiclone.
4. Antihistamines used for sleep: Diphenhydramine, Doxylamine
5. Melatonin.
6. Nitric oxide synthase (NOS)-benzodiazepine.
7. NOS-sleep medication/sedative/hypnotic otherwise unknown.

TABLE 3a. **PROMIS sleep disturbance short form**

In the past 7 days…	
1. I had a hard time concentrating because of poor sleep	Not at all, a little bit, somewhat, quite a bit, very much
2. I had problems during the day because of poor sleep	Not at all, a little bit, somewhat, quite a bit, very much
3. I had a hard time getting things done because I was sleepy	Not at all, a little bit, somewhat, quite a bit, very much
4. I felt irritable because of poor sleep	Not at all, a little bit, somewhat, quite a bit, very much
5. I felt tired	Not at all, a little bit, somewhat, quite a bit, very much
6. I was sleepy during the daytime	Not at all, a little bit, somewhat, quite a bit, very much
7. I had trouble staying awake during the day	Not at all, a little bit, somewhat, quite a bit, very much
8. I felt alert when I woke up. (reverse Likert-scale)	Very much, quite a bit, somewhat, quite a bit, very much

The 8-item PROMIS Sleep Disturbance Short Form item bank includes eight items that assess perceptions of sleep quality, sleep depth and restoration from sleep over the past 7 days. Respondents rate various aspects of their sleep over the past 7 days on 5-point scales. Raw scores range from 8 to 40 and higher scores on the scale indicate more disturbed sleep.
Sleep disturbance severity is rated as follows for the corresponding T-score: "None to slight" (T-score less than 55), "Mild" (55.0-59.9), "Moderate" (60-69.9), and "Severe" (70 and over).[10]

TABLE 3b. **Jenkins Sleep Scale (JSS)**

How often during the previous 4 weeks did you have the following symptoms:	
1. Difficulty falling asleep	Not at all, 1-3 n.ghts, 4-7 nights, 8-13 nights, 15-21 nights, 22-28 nights
2. Waking up several times per night	Not at all, 1-3 nights, 4-7 nights, 8-13 nights, 15-21 nights, 22-28 nights
3. Difficulty staying asleep (including waking up too early)	Not at all, 1-3 nights, 4-7 nights, 8-13 nights, 15-21 nights, 22-28 nights
4. Waking up feeling tired and worn out after usual amount of sleep	Not at all, 1-3 nights, 4-7 nights, 8-13 nights, 15-21 nights, 22-28 nights

The Jenkins Sleep Scale consists of 4 questions that ask subjects to rate different aspects of their sleep over the past 4 weeks on 6-point scales. Sleep disturbances are considered when scoring 4 or more on the JSS.[9]

measures ANOVA was used to analyze change in each measure (IPSS, PROMIS-SDSF, JSS) as a function of gender, time, and gender time interaction. To assess significance, post hoc tests were performed, controlling for multiple comparisons. Spearman's rho was used to assess correlations. The proportion of subjects who obtained improvements in sleep scores (i.e., JSS > 3 point improvement) was also compared separately. Significance was assumed when $p < 0.05$.

Results

Baseline characteristics are noted in Table 4. Briefly, 34 subjects met the inclusion criteria: 21 male and 13 female. Twenty-six remained at the follow up visit. There was no difference between male and females in baseline demographics as assessed by t-test or non-parametric equivalent.

Sleep measure outcomes

At screening, the mean PROMIS-SDSF was 26.5 ± 1.2 points, corresponding to a "Mild" sleep disturbance across all subjects, Figure 1. There was no gender effect. The greatest sequential decrease in PROMIS scores occurred between screening and visit 2 (-5.7 points). By the follow up visit the average PROMIS sleep score had dropped to 19.3 (-7.2 points), which corresponds to a T-score of 49.0 and translates a sleep disturbance level of "None to slight." This improvement from mild to none sleep disturbance supports the original

TABLE 4. **Baseline characteristics, IPSS scores, PROMIS-SDSF, and JSS scores**

	Total	**Male**	**Female**
Subjects	34	21	13
Age (mean ± SE)	64.1 ± 2.0	64.0 ± 2.6	64.2 ± 3.3
BMI (kg/m^2, mean ± SE)	28.8 ± 1.0	27.9 ± 1.4	30.3 ± 1.4
PVR (mL, mean)	37.3 ± 7.2	35.2 ± 8.7	40.7 ± 13.1
Race			
Caucasian	31	19	12
African American	2	1	1
Other	1	1	0
IPSS (mean ± SE)	21.0 ± 0.9	21.0 ± 1.1	21.0 ± 1.6
IPSS-Q1-6 (mean ± SE)	17.4 ± 0.9	17.6 ± 1.1	17.3 ± 1.6
IPSS-Q7** (mean ± SE)	3.5 ± 0.2	3.4 ± 0.2	3.7 ± 0.4
PROMIS-SDSF (mean ± SE)	26.5 ± 1.2	25.7 ± 1.5	27.8 ± 2.0
Jenkins sleep scale (mean ± SE)	14.1 ± 0.6	13.6 ± 0.7	15.0 ± 1.0
Voiding diary (voids/day) (mean ± SE) (mean ± SE)	11.6 ± 0.4	11.5 ± 0.5	11.7 ± 0.7
Voids/night* (mean ± SE)**	**2.5 ± 0.2**	**2.5 ± 0.3**	**2.7 ± 0.5**
SBP (mean mmHg ± SE)	134.0 ± 2.8	132.8 ± 3.6	135.8 ± 4.5
DBP (mean mmHg ± SE)	81.1 ± 1.4	82.5 ± 1.7	78.8 ± 2.1
Heart rate (mean bpm ± SE)	72.4 ± 2.3	73.7 ± 3.2	70.2 ± 2.9

IPSS = International Prostate Symptom Score; PROMIS-SDSF = Patient-Reported Outcome Measurement Information System Sleep Disturbance Short Form; JSS = Jenkins Sleep Scale; BMI = body mass index; PVR = post-void residual; SBP = systolic blood pressure; DBP = diastolic blood pressure
There was no difference between male and female in baseline demographics as assessed by t-test or non-parametric equivalent.
**derived from question 7 of the IPSS
***derived from voiding diary

hypothesis that mirabegron use induces a rapid and sustained improvement in sleep quality.

All 34 subjects completed the JSS at the screening visit with a mean score of 14.1 ± 0.6. The greatest sequential improvement in JSS occurred between drug initiation and visit 2, Figure 2. By the follow up visit, the average JSS was 8.3 ± 0.9, indicating net decrease of -5.8 points. This finding also supports the original hypothesis that mirabegron use induces a rapid and sustained improvement in sleep quality. There was no gender impact.

LUTS outcomes

At screening visit all 34 subjects completed the IPSS with a mean score of 21.0 ± 0.9. After starting mirabegron the mean IPSS decreased 6.2 points to 14.8 (±_1.0) by visit 2. The lowest mean IPSS was logged at visit 4 (11.3 ± 1.2), representing a decrease in 9.7 points from the screening visit. At the follow up visit the mean IPSS was 12.4 ± 1.3, depicting a net decrease of 8.6 points. Overall, these reductions in IPSS were statistically significant at each study visit, Figure 3.

Mean IPSS decreased 8.6 points from screening visit (21.0) to follow up visit (12.4). The difference in IPSS decreases between females and males was not significant. This supports the idea that mirabegron use induces a rapid and significant improvement in LUTS regardless of gender.

Questions 1-6 of the IPSS address voiding and storage symptoms, whereas question 7 specifically queries nocturia. In order to better delineate the impact of mirabegron on nocturia versus other LUTS complaints, we evaluated how it changed subjects' IPSS for Question 7 relative to Questions 1-6. Using this delineation, there was a mean decrease of 7.3 points from the screening to the follow up visit for IPSS Questions 1-6 (IPSS Q1-6), with visit 4 having the greatest absolute mean decrease (-8.5 points), Figure 4.

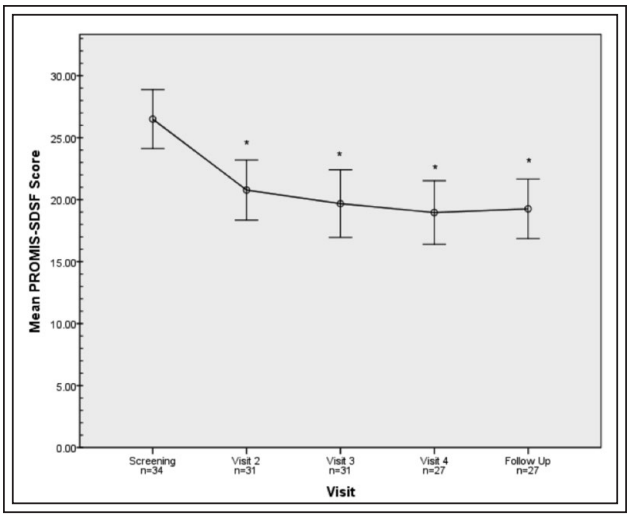

Figure 1. PROMIS-SDSF scores over time. Error Bars: +/- 2 SE, * p values < 0.0001 when comparing 'Visit' to initial screening after adjusting for multiple comparisons. The PROMIS-SDSF item bank has been validated as the most accurate measure for adults and includes eight items that assess perceptions of sleep quality, sleep depth, and restoration from sleep over the past 7 days[11]. We found statistically significant decreases of PROMIS-SDSF scores (improved quality of sleep) from screening to each of the subsequent visits through follow up ($p < 0.0001$ for all). There was no gender effect.

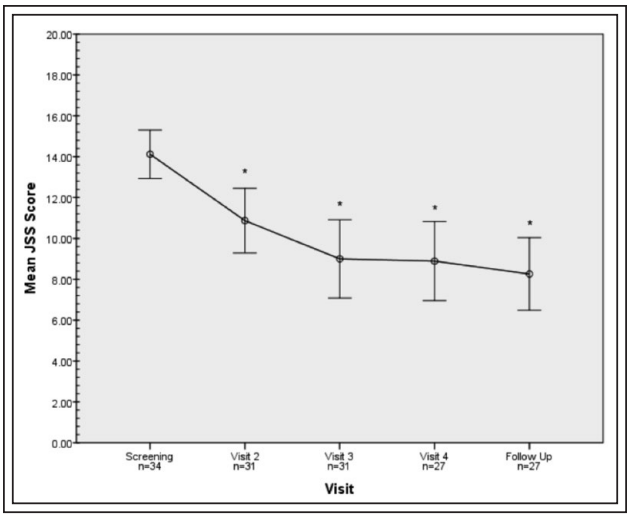

Figure 2. Jenkins Sleep Scale (JSS) scores over time. Error Bars: +/-2 SE, * p values < 0.0001 when comparing 'Visit' to initial screening after adjusting for multiple comparisons. Similar to PROMIS-SDSF, there were statistically significant decreases in JSS from the screening visit to each subsequent visit through the final follow up ($p < 0.0001$ for all). Additionally, there was a statistically significant decrease in average JSS between Visit 2 and follow up ($p = 0.0285$). There was no gender impact.

Based on IPSS Question 7 (IPSS Q7), the mean number of nighttime voids was 3.5 (± 0.2) with a mean decrease from screening to follow up visit of -1.3 voids. Furthermore, the frequency of nocturia decreased at each visit relative to the visit before.

In order to ascertain if mirabegron had a preferential effect on nocturia on our cohort, we calculated the percent change for each visit for both Questions 1-6 and Question 7 (paired t-test). There were no statistically significant differences in percent change between Questions 1-6 and Question 7 for any of the visits.

Voiding diary outcomes

Study subjects completed 24-hour voiding diaries for all visits. Participants logged an average of 11.6 ± 0.4 voids per day (VPD) at screening. After starting mirabegron there was a mean decrease of 1.5 VPD at visit 2 to 10.1 ± 0.5. By the follow up visit, subjects logged 9.7 ± 0.5 VPD to denote a net statistically significant decrease of -1.9 VPD, Figure 5. There was no gender impact.

We analyzed the voiding diaries to examine the mean number of nighttime voids, i.e. nocturic events. At screening, study subjects reported an average of 2.5 ± 0.2 episodes of nocturia. The average nocturic

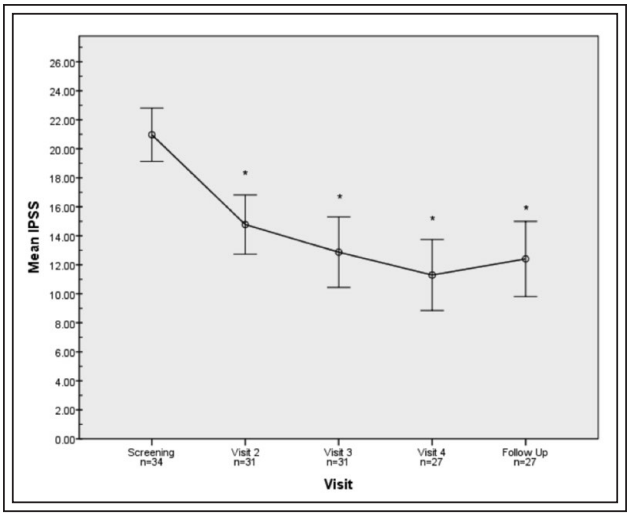

Figure 3. Total IPSS over time. Error Bars: +/- 2 SE, * p values < 0.0001 when comparing 'Visit' to initial screening after adjusting for multiple comparisons. Overall, the reduction in IPSS persisted through the conclusion of the study. These changes were statistically significant between the screening and each of the subsequent visit ($p < 0.0001$ for all), as well as between Visit 2 and Visit 4 ($p = 0.0105$). The difference in IPSS decreases between females and males was not significant.

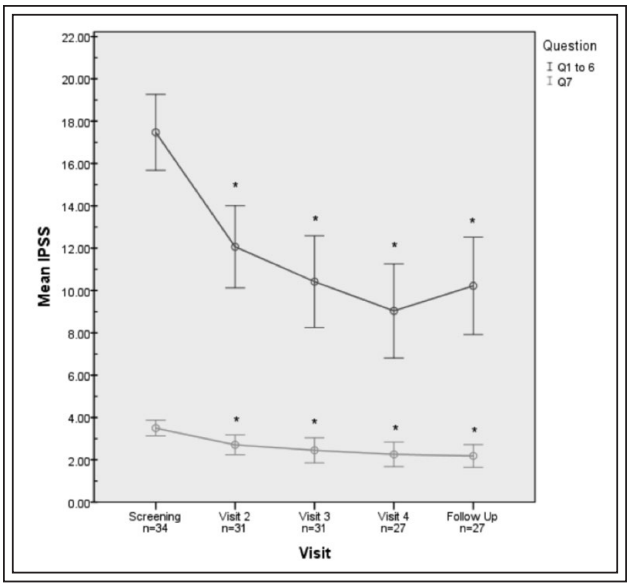

Figure 4. IPSS for Questions 1-6 and Question 7 over time. Error Bars: +/- 2 SE, * p values < 0.0001 when comparing 'Visit' to initial screening after adjusting for multiple comparisons.
Statistical significance was maintained for IPSS Questions 1-6 between the screening and each subsequent visit ($p < 0.0001$ for all), as well as between Visit 2 and Visit 4 ($p < 0.0018$). There was a statistically significant difference in Question 7 scores between the screening visit and each subsequent visit ($p < 0.0001$ for all). In order to ascertain if mirabegron had a preferential effect on nocturia on our cohort, we calculated the percent change for each visit for both Questions 1-6 and Question 7 (paired t-test). There were no statistically significant differences in percent change between Questions 1-6 and Question 7 for any of the visits.

episodes either remained stable or continued to decrease with each successive visit (1.9 ± 0.3 visit 2, 1.9 ± 0.3 visit 3, 1.7 ± 0.2 visit 4), Figure 6.

We also examined the percentage of nighttime voids to overall voids. On average, nocturic episodes comprised 21.4% of all daily voids at screening. This decreased to 17.5%, 16.2%, and 15.9% at visits 2, 3, and 4, respectively. A statistically significant decrease in percentage of night voids was reached between screening and visit 3 ($p = 0.0232$) and visit 4 (0.0364) (data not shown).

Nocturnal polyuria

Through the voiding diaries, we were able to see how many patients had nocturnal polyuria (defined as > 33% daily urine output at night). At the screening visit, 9 of our 34 study subjects had nocturnal

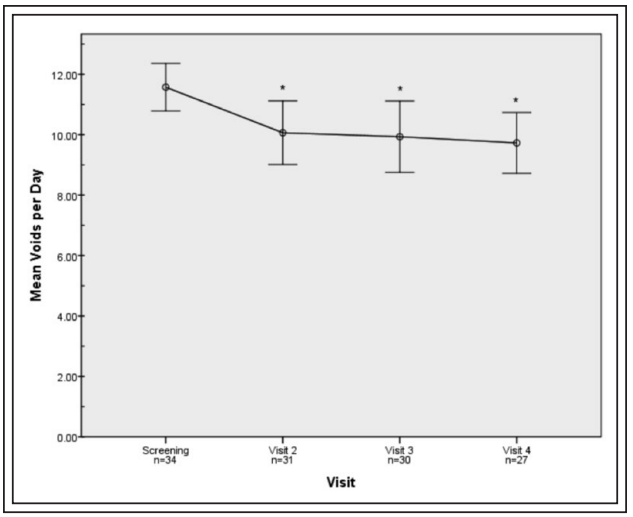

Figure 5. Mean voids per day (VPD) over time. Error Bars: +/-2 SE, * p values < 0.01 when comparing 'Visit' to initial screening after adjusting for multiple comparisons, (p values are 0.002, 0.001, and 0.002, respectively).
Pairwise comparison showed statistically significant decreases between the mean VPD at screening versus VPD at each subsequent visit ($p = 0.0032$ Visit 2, $p = 0.0027$ Visit 3, $p = 0.0024$ Visit 4). There was no gender impact.

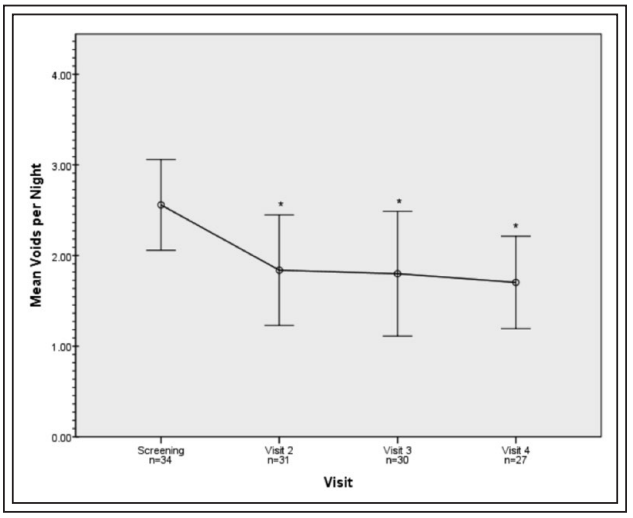

Figure 6. Mean episodes of nocturia. Error Bars: +/- 2 SE, * p values < 0.05 when comparing 'Visit' to initial screening after adjusting for multiple comparisons, (p values are 0.024, 0.016, and 0.028, respectively). Statistical significance was reached between the screening visit and each subsequent visit ($p = 0.0236$ Visit 2, $p = 0.0157$ Visit 3, $p = 0.0276$ Visit 4). Overall, there was a mean decrease of -0.8 nighttime voids from screening to follow up.

polyuria (data not shown). By the follow up visit, 6 out of 9 of these patients no longer exhibited nocturnal polyuria. Of note, the average percentage of nighttime urine output at screening for these 6 patients was 50.5%, which decreased to 16.8% by the follow up (-33.7% nighttime urine output from screening to follow up).

Conversely, 2 of 9 patients with nocturnal polyuria at screening persisted with it at follow up. There was no substantial difference in the percentage of these 2 patients' nighttime urine volumes at screening and follow up. One of the 9 patients with nocturnal polyuria did not complete the voiding diary at follow up, but was noted to have resolution of nocturnal polyuria at visits 2 and 3. Taken as a whole, these results suggest that mirabegron may indeed reduce nighttime urinated volumes in patients with nocturnal polyuria.

Additionally, we assessed if the presence or absence of nocturnal polyuria had any significant effect on the survey responses for the PROMIS-SDSF, JSS, IPSS, or IPSS Q7. Our analysis revealed mixed results with 5 out of 16 visits showing statistical significance. Overall, however, there was no clear trend to report.

IPSS Q7 versus voiding diary

We wanted to assess the correlation between the IPSS Q7 (nocturia) versus the reported nighttime voids drawn from the voiding diary. Intuitively, these measures should be highly correlated as they address the same important complaint that patients most commonly rate as a chief complaint and the symptom least likely to improve with any behavior therapy, medication, or surgery. In examining this comparison, we noted that higher IPSS Q7 responses were significantly associated with higher nighttime voids as drawn from the diaries, data not shown. IPSS Q7 and number of nighttime voids were significantly correlated at all visits (Spearmans $r = 0.55$, $p = 0.001$ [screening visit], 0.87, $p < 0.0001$ [visit 2], 0.80, $p < 0.0001$ [visit 3], and 0.62, $p = 0.001$ [visit 4]). This suggests excellent fidelity between these two measures of an important outcome for this study.

IPSS Q7 and storage subscale score

The IPSS storage subscale score is defined as the sum of IPSS Questions 2, 4, and 7 (frequency, urgency, and nocturia). We looked at the ratio of IPSS Q7 to the storage subscale score in order to evaluate if mirabegron had a preferential effect on nocturia versus a preferential effect on all storage symptoms. Indeed, there was no significant change over time, suggesting that mirabegron may reduce nocturia by reducing all bladder storage symptomology (data not shown).

IPSS frequency and urgency components

We also separately examined the frequency and urgency components of the IPSS, since patients may have had onset of voiding symptoms while on mirabegron. Our analysis showed that frequency scores decreased from 4.1 at screening to 2.7 at follow up ($p < 0.0001$). Likewise, urgency scores decreased from 3.6 at screening to 2.1 at follow up ($p < 0.0001$). These findings support the established notion that mirabegron improves all storage symptoms (data not shown).

TABLE 5. **Quality of life in regards to lower urinary tract symptoms**

Quality of life	**Screening %**	**Follow up %**
Mostly satisfied, pleased, or delighted	0.0	29.6
Mixed, mostly dissatisfied, unhappy, or terrible	99.9	70.3

TABLE 6. **Adverse events of mirabegron**

Adverse event	**n = 17 patients**	**Relationship to study drug and action taken**
Headache	3	Possible (drug removed permanently for 1 patient)
Fainting	1	Suspected (drug removed permanently for 1 patient)
Higher blood pressure	1	Suspected (no action taken)
Ureteral stone	1	Not suspected (drug removed permanently for 1 patient)

QoL outcomes

Study subjects completed a questionnaire at each visit rating their QoL in regard to their LUTS (IPSS Question 8). At screening, all patients rated their QoL as "Mixed," "Mostly dissatisfied," "Unhappy," or "Terrible." By the follow up visit, 29.6% of subjects rated their quality of as "Mostly satisfied," "Pleased," or "Delighted." Specifically, there was an increase from 0% to 3.7%, 14.8%, and 11.1% in subjects that were "Delighted," "Pleased," and "Mostly satisfied," respectively, with the improvement in their LUTS. The "Unhappy" category decreased from 35.3% to 14.8%. Subjects who initially rated their quality of life as "Terrible" decreased from 17.6% to 7.4%, Table 5.

Adverse events

There were 29 adverse events reported in 17 patients, none of which were classified as serious adverse events (SAE). Twenty-eight of these 29 events were described as mild or moderate in severity. Of these 29 events, 5 (17.2%) were considered possibly or suspected to be related to the study drug, Table 6. Of the 29 adverse events, only 3 (10.3%) resulted in removal of the drug permanently, while the rest were regarded as not applicable or drug dose not changed.

Discussion

The critical role of organized sleep in overall health and QoL cannot be overstated. In a similar fashion, the relationship between sleep and LUTS is important to recognize given how the two can be interrelated, despite little evidence in the literature. In particular, nocturia necessarily disrupts the normal sleep cycle by interfering with sleep efficiency and prolonging sleep latency, which inevitably causes a negative impact on one's health and QoL.

Sleep

Novel to this report, we evaluated sleep disturbance using two sleep assessment questionnaires: the JSS and the PROMIS-SDSF. The PROMIS-SDSF item bank has been validated as the most accurate measure for adults and includes eight items that assess perceptions of sleep quality, sleep depth, and restoration from sleep over the past 7 days.[11] The PROMIS-SDSF was chosen as our primary sleep outcome measure due to the potential for a greater level of measurement precision when compared to other available sleep disturbance scales.[8,11,12] Furthermore, the PROMIS-SDSF has been shown to have superior measurement precision when compared to both the Pittsburgh Sleep Quality Index and Epworth Sleepiness Scale, as demonstrated by greater test information values across the continuum of sleep disturbance severity despite having fewer total items, a crucial advantage for both research and clinical applications.[12]

The present study showed significant decreases of scores (improved sleep quality) from screening to each subsequent visit through follow up for both the PROMIS-SDSF and JSS ($p < 0.0001$ for all). Importantly, subjects showed clinically significant improvement from "Mild" to "None to slight" sleep disturbance based on the PROMIS-SDSF results. Although there are no known clinically important differences in the JSS as there are in the PROMIS-SDSF scales, the fact that the JSS change was greater than one half of a standard error of the mean makes its clinical relevance profound. These findings supports our original hypothesis that mirabegron can produce a rapid and sustained improvement in quality of sleep. Additionally, these findings were echoed in the QoL questionnaire. At screening virtually all patients felt mixed, mostly dissatisfied, unhappy, or terrible regarding their QoL. By the follow up visit 29.6% experienced a progression into the mostly satisfied, pleased, or delighted categories. Together, these findings offer quantitative and qualitative support for our original hypothesis that mirabegron improves nocturia and sleep measures.

Since our study did not include a placebo arm, we were interested in seeing what the literature showed regarding the placebo effect on sleep studies involving other medications. A literature search revealed three notable studies. In a double-blind, randomized trial Sletten et al investigated the effect of melatonin 0.5 mg on improving sleep disturbance using the PROMIS sleep scale over the course of 4 weeks.[13] Those receiving melatonin 0.5 mg experienced an average -3.6 point decrease from their baseline, whereas the placebo group essentially experienced a +0.3 point increase from their baseline. By comparison, in our study patients experienced an average -5.8 point decrease by week 4 on the PROMIS-SDSF. Of note, patients in the Sletten et al study had a similar baseline PROMIS-SDSF score as our study.

In a large, double-blind, parallel group study Spaeth et al explored how sodium oxybate improves sleep using the JSS in those with fibromyalgia over a 14-week course.[14] Subjects' baseline JSS score was 16.0, compared to 14.3 in our study. On average, subjects receiving sodium oxybate 4.5 grams/night had a -4.0 point decrease, whereas those receiving 6 grams/night had a -5.0 decrease. Conversely, the placebo group only experienced a -1.0 point decrease. Comparing this to our study, we observed an average -6.0 point decrease in the JSS.

Finally, in a randomized-controlled trial Deodhar et al examined how golimumab in 50 mg or 100 mg subcutaneous doses impacts sleep disturbance in patients with ankylosing spondylitis using the JSS over 24 weeks.[15] Patients were assessed patients at baseline, 14 weeks, and 24 weeks. Since our study was 12 weeks in length, we compared our findings to their results at 14 weeks, rather than 24 weeks. Subjects experienced a -3.0 point decrease at 14 weeks whether they were taking golimumab 50 mg or 100 mg doses. On the contrary, those receiving placebo had a -0.0 point decrease on the JSS.

Taken together, we conclude from our literature review that placebos have a rather modest, if any, effect on the PROMIS-SDSF and JSS questionnaires. This finding further substantiates our study's premise that mirabegron improves sleep measures in those with lower urinary tract symptoms associated with disordered sleep.

Nocturia

Nitti et al investigated the effect of mirabegron in a large, pooled efficacy analysis of three randomised, double-blind, placebo-controlled, phase III studies.[16] The primary endpoints they investigated were mean number of incontinence episodes per 24 hours and mean number of micturitions per 24 hours. Overall, both our study and Nitti et al demonstrated the well-established notion that mirabegron improves LUTS. However, a notable difference can be seen in regards to nocturia outcomes. Their baseline statistics showed a mean of roughly 2.2 nighttime micturitions. They compared a placebo group to 50 mg and 100 mg doses of mirabegron that showed statistically significant adjusted changes from baseline at 12 weeks of -0.42, -0.55, and -0.54, respectively ($p < 0.05$). In contrast, our cohort had a baseline of 3.5 nocturic episodes at screening and our cohort received 25 mg mirabegron that was increased to 50 mg at 4 weeks. Our change from baseline in nocturic events was significantly greater at -1.3 at 12 weeks ($p < 0.0001$). Without the inclusion of a placebo group, this discrepancy remains unclear, but may partly be attributed to differences in inclusion/exclusion criteria and baseline severity.

Recently, Yoshida et al explored the effect of 50 mg mirabegron on sleep quality using the Pittsburgh Sleep Quality Index in female OAB patients.[17] Similar to our study, this investigation had a small cohort and lacked a placebo group. Baseline characteristics showed 2.5 nocturnal micturitions that decreased by -0.6 to 1.9 nocturic events after 12 weeks of treatment ($p < 0.05$). Total IPSS decreased from 12.4 to 7.3 after 12 weeks (-5.1 points). In contrast, our study of both female and male subjects showed an IPSS decrease of -11.0 in females and -8.6 points in both genders. Their study also supports the idea that mirabegron can specifically target nocturia, the LUTS complaint that many consider to be the most difficult to treat by any modality. Notably, the other class of medications shown to significantly treat nocturia have been the vasopressin analogues, including oral and nasal spray forms. A recent pooled analysis of two randomized, double-blind, placebo-controlled phase 3 trials examining vasopressin analogue nasal spray showed decreases of -1.2, -1.4, and -1.5 nocturic events for placebo, 0.83 mcg intranasal dosing ($p < 0.0001$), and 1.66 mcg intranasal dosing ($p < 0.0001$).[18]

IPSS and voiding diaries

We previously performed a longitudinal population-based study addressing how LUTS and sleep disorders may be causally related.[5] Sleep restriction, restless sleep, sleep medication use, and LUTS were assessed by self-reports in a prospective cohort study of men and women who completed the Boston Area Community Health (BACH) survey. In a follow up survey, 10.0% reported new LUTS, 8.5% urinary incontinence (UI), and 16.0% reported nocturia. Incidence of poor sleep quality was 24.2%, sleep restriction 13.3% and sleep medication use was 11.6%. Controlling for confounders, poor sleep quality and sleep restriction exhibited consistent positive associations with incident urologic symptoms, but in contrast, only nocturia was positively associated with incident sleep disturbances. In support of our previous work, in this separate population-based cohort, self-reported sleep disturbances and LUTS are linked with one another bi-directionally. Based on this supposition, it is reasonable to believe that successful treatment of LUTS can improve sleep behavior and vice versa.[3]

In this trial, our analysis revealed mirabegron had a positive impact on LUTS as evidenced by decreased IPSS from an average of 21.0 points at screening to 12.4 points at the follow up visit. This finding is important as it denotes a categorical shift from clinically "severe" to "moderate" LUTS. Notably, the reduction in IPSS persisted through the conclusion of the study at 12 weeks, suggesting that mirabegron use produces a rapid, durable, and clinically significant improvement in LUTS regardless of gender.

When examining IPSS Q1-6 and IPSS Q7 separately, we found that both significantly decreased during each subsequent visit when compared to the screening visit. Moreover, mean scores for Q7 continued to decrease from screening to each subsequent visit.

While Questions 1-6 also showed a persistent decline from screening through visit 4, this effect appeared to plateau by the follow up visit. This raises the possibility of a preferential effect of mirabegron on nocturia, which would be a novel finding amongst current medications to treat LUTS. Furthermore, the continual decline mirabegron had on nighttime voids lasting through the follow up visit suggests a durable effect on improving nocturia that may have persisted past the study's duration.

When comparing IPSS Q7 to IPSS Q1-6, however, we found there was no statistically significant difference in percent change between the two for any visit comparison. Interestingly, however, mirabegron effected an earlier onset of change for IPSS Questions 1-6 compared to Question 7, as evidenced by our data showing a slower onset of effect for Question 7, (data not shown). The mechanism of action for this difference remains unclear. One possible explanation is that binding beta-3 receptors in the smooth muscle of the bladder causes more immediate and noticeable improvements in OAB symptoms, whereas the effect of increasing bladder capacity and compliance, thus decreasing nighttime voids, takes longer to achieve due to the need for what is essentially bladder remodeling. Additionally, because B3 adrenergic receptor agonists help with urgency sensation this could help the patients with nocturia due to bladder related issues.

From the voiding diaries we noted that voids per day decreased from 11.6 to 9.7 and nighttime voids decreased from 2.5 to 1.7, both of which met statistical significance. In contrast to our IPSS Q1-6 and IPSS Q7 findings that hinted a preferential effect on nocturia, this relatively split impact on daytime and nighttime voids (-1.1 daytime voids, -0.8 nighttime voids) suggests a potentially nonselective temporal effect of mirabegron. Indeed, our and others prior research has shown that improving sleep can influence both daytime and nighttime LUTS and this bi-directional relationship should be emphasized.[5,19] A study with more power and longer follow up would be needed to elucidate this discrepancy.

Similarly, our analysis of study subjects with nocturnal polyuria showed encouraging results. Roughly one-quarter of our patients exhibited nocturnal polyuria at screening, and 66% of these patients showed an average decrease of 33.7% in nighttime urine output from screening to follow up. Certainly a larger-scale study would be needed to confirm our findings, but this nonetheless shows promise that mirabegron may be an effective treatment in those with nocturnal polyuria.

Limitations

The main limitations of this study are that it was an unblinded single-center study and there was no placebo-control group. It should be noted that there is a large placebo effect among patients with LUTS and that this effect may play a role in our findings. This study was conducted as a pilot, without a placebo arm, in order to evaluate if mirabegron had an effect on sleep measures and nocturia that merited further research and funding on a larger scale, including the addition of a placebo comparison arm. Nevertheless, our study design was rigorous and the results support the notion that mirabegron can treat patients with nocturia and simultaneously improve sleep quality. Furthermore, this is the first study to evaluate sleep measures using the PROMIS sleep scale, which has been validated as the most accurate sleep measure for adult subjects. A randomized large-scale, placebo-controlled study is needed to more definitively establish the extent to which mirabegron improves nocturia and sleep.

Conclusion

This study showed that mirabegron improves nocturia, LUTS, and sleep measures in males and females with urinary symptoms associated with disordered sleep. These results were validated using well-established measures including the IPSS, Jenkins and PROMIS sleep scales, voiding diaries, and quality of life questionnaires. □

References

1. Holm-Larson T. The economic impact of nocturia.*Neurourol Urodyn* 2014;33(Suppl 1):S10-S14.
2. Cakir OO, McVary KT. LUTS and sleep disorders: emerging risk factor. *Curr Urol Rep* 2012;13(6):407-412.
3. Helfand BT, Lee JY, Sharp V et al. Associations between improvements in lower urinary tract symptoms and sleep disturbance over time in the CAMUS trial. *J Urol* 2012;188(6): 2288-2293.
4. Helfand BT, McVary KT, Meleth S et al. The relationship between lower urinary tract symptom severity and sleep disturbance in the CAMUS trial. *J Urol* 2011;185(6):2223-2228.
5. Araujo AB, Yaggi HK, Yang M et al. Sleep-related problems and urologic symptoms: Testing the hypothesis of bi-directionality in a longitudinal, population-based study. *J Urol* 2014;191(1):100-106.

6. Suarez O, Osborn D, Kaufman M et al. Mirabegron for male lower urinary tract symptoms. *Curr Urol Rep* 2013;14(6):580-584.
7. Sung VW, Marques F, Rogers RR et al. Content validation of the patient-reported outcomes measurement information system (PROMIS) framework in women with urinary incontinence. *Neurourol Urodyn* 2011;30(4):503-509.
8. Jenkins CD, Stanton BA, Niemcryk SJ et al. A scale for the estimation of sleep problems in clinical research. *J Clin Epidemiol* 1988;41(4):313-321.
9. American Psychiatric Association. 2013. PROMIS, Sleep Disturbance, Short Form, American Psychiatric Association. Retrieved from: https://www.psychiatry.org/File%20Library/Psychiatrists/Practice/DSM/APA_DSM5_Level-2-Sleep-Disturbance-Adult.pdf
10. Reis C, Mestre C, Tecedeiro M et al. Translation, cross-cultural adaptation and psychometric properties of the Jenkins Sleep Scale in a sample of shift workers. *Lab Psicol* 2014;12(2):89-98.
11. Buysse DJ, Yu L, Moul DE et al. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. *Sleep* 2010;33(6):781-792.
12. Yu L, Buysse D, Germain A et al. Development of short forms from the PROMIS™ sleep disturbance and sleep-related impairment item banks. *Behav Sleep Med* 2011;10(1):6-24.
13. Sletten TL, Magee M, Murray JM et al. Efficacy of melatonin with behavioural sleep-wake scheduling for delayed sleep-wake phase disorder: A double-blind, randomised clinical trial. *PLoS Med* 2018;15(6):e1002587
14. Spaeth M, Bennett RM, Benson BA et al. Sodium oxybate therapy provides multidimensional improvement in fibromyalgia: Results of an international phase 3 trial. *Ann Rheum Dis* 2012;71(6):935-942.
15. Deodhar A, Braun J, Inman RD et al. Golimumab reduces sleep disturbance in patients with active ankylosing spondylitis: Results from a randomized, placebo-controlled trial. *Arthritis Care Res* 2010;62(9):1266-1271.
16. Nitti V, Khullar V, van Kerrebroeck P et al. Mirabegron for the treatment of overactive bladder: a prespecified pooled efficacy analysis and pooled safety analysis of three randomised, double-blind, placebo-controlled, phase III studies. *Int J Clin Pract* 2013;67(7):619-632.
17. Yoshida M, Gotoh M, Kageyama S et al. Mirabegron improves nocturia, nocturia-associated quality of life, and sleep quality in female patients with overactive bladder. *Austin J Urol* 2017; 4(1):1054.
18. Kaminetsky J, Fein S, Dmochowski R et al. Efficacy and safety of SER120 nasal spray in patients with nocturia: pooled analysis of 2 randomized, double-blind, placebo controlled, phase 3 trials. *J Urol* 2018;200(3):604-611.
19. Shao I-Hung, Wu Chia-Chen, Hsu Hueih-Shing et al. The effect of nocturia on sleep quality and daytime function in patients with lower urinary tract symptoms: a cross-sectional study. *Clin Interv Aging* 2016;11:879-885.