

# Outcomes of pharmacological management of nocturia with non-antidiuretic agents: does statistically significant equal clinically significant?

**Ariana L. Smith and Alan J. Wein**

*Division of Urology, Hospital of University of Pennsylvania, Philadelphia, PA, USA*

Accepted for publication 31 August 2010

To evaluate the statistical and clinical efficacy of the pharmacological treatments of nocturia using non-antidiuretic agents. A literature review was carried out on the treatments of nocturia specifically addressing the impact of alpha blockers, 5-alpha reductase inhibitors (5ARI) and antimuscarinics on a reduction in nocturnal voids. Despite commonly reported statistically significant results, nocturia has shown a poor clinical response to traditional therapies for benign prostatic hyperplasia including alpha blockers and 5ARI. Similarly, nocturia has shown a poor clinical response to traditional therapies for an overactive bladder including antimuscarinics. Statistical

## What's known on the subject? and What does the study add?

Standard therapies for nocturia, including alpha blockers, 5-alpha reductase inhibitors and antimuscarinics have shown statistically significant improvements in nocturnal voiding episodes in several clinical trials. Clinically significant results, however, have not been achieved with most studies showing a reduction of a half a void or less per night. Alternative therapeutic options for this bothersome condition are needed.

success has been achieved in some groups with a variety of alpha blockers and antimuscarinic agents, but the clinical significance of these changes is doubtful. It is likely that other types of therapy will need to be employed in order to achieve a clinically significant reduction in nocturia.

## KEYWORDS

nocturia, benign prostatic hyperplasia, overactive bladder, alpha blockers, 5-alpha reductase inhibitors

## INTRODUCTION

Nocturia is defined by the 4<sup>th</sup> International Consultation on Incontinence as the need to wake from sleep one or more times to void [1]. Given the impact on sleep, nocturia is often associated with a great degree of bother and decrement in quality of life. It also has a significant negative impact on health-related quality of life (HRQL). In fact, individuals who experience two or more episodes of nocturia nightly may have serious consequences including falls, fractures and sleep deprivation with a detrimental impact on mood, productivity at work and overall health [2]. Using a conservative definition of two or more voids per night, approximately 10% to 20% of young adults and 25% to 40% of older adults experience the condition [3].

Nocturia has long been considered a symptom secondary to underlying bladder or prostate dysfunction. As a result, therapies have been aimed at ameliorating these conditions. Recently, however, nocturia has been appreciated as an independent condition, in addition to a component of various types of lower urinary tract dysfunction [1]. Non-urological aetiologies of

nocturia include polyuria, congestive heart failure, sleep apnoea, restless leg syndrome, peripheral vascular disease, sleep disorders, nighttime food ingestion and excessive fluid intake. Classification of nocturia, including polyuria, nocturnal polyuria and bladder storage disorders, can generally be made using urinary frequency volume charts and can help direct therapy.

The present review addresses the results of treatment for nocturia with drugs directed towards lower urinary tract dysfunction including BPH and overactive bladder (OAB). While many of these studies have shown statistical significance in decreasing nocturia, and these therapies continue to be the mainstay of treatment, clinically, patients fail to achieve meaningful response.

## THERAPIES USED FOR THE MANAGEMENT OF BENIGN PROSTATIC HYPERPLASIA

A number of studies have addressed the impact of alpha blockers, 5-alpha reductase inhibitors (5ARI) and combination therapy on nocturia. The effect of tamsulosin 0.4 mg was assessed in men with BPH who experience

two or more nocturnal voids and was found to statistically improve the mean IPSS for nocturia compared with placebo [4]. The statistically significant reduction, however, resulted in a minimal absolute difference between placebo and tamsulosin with a mean change of 3.1 to 2.3 nighttime voids for placebo and 3.1 to 2.0 for tamsulosin. The sleep latency, or the time to the first awakening to void, was not found to be statistically different in this study. In a secondary analysis of the Veterans' Administration Cooperative Study, 1078 men with BPH, mean age 45–80 years, were assessed for a reduction in nocturia measured by the IPSS [5]. The study had four arms, terazosin, finasteride, combination terazosin plus finasteride and placebo. In all, 96.5% of patients had nocturia once or more and 75.8% had nocturia twice or more per night. The improvement in nocturia episodes is shown in Table 1. A 50% reduction in nocturia was defined as a meaningful benefit by the authors of this previous study, and this definition allowed achievement of statistically significant differences in response rates by treatment arm. In reality, however, this represented only a 17% greater improvement in nocturia for terazosin over placebo.

TABLE 1 Changes in nocturia from medication treatment for benign prostatic hyperplasia from the Veterans' Administration Cooperative Study (5)

	<i>n</i>	Baseline nocturia	Nocturia after 1 year of therapy	<i>n</i> ≥ 2 Nocturia	Baseline nocturia	Per cent with 50% reduction in nocturia
Terazosin	262	2.4	1.8*	199	2.9	39%*
Finasteride	252	2.5	2.1	205	2.8	25%
Combination	272	2.5	2.0†	195	2.9	32%†
Placebo	254	2.4	2.1	189	2.9	22%

\*Statistically significantly different from the other three groups. †Statistically significantly different from finasteride alone and from placebo.

TABLE 2 Changes in nocturia from the medical treatment of prostatic symptoms trial (6)

	<i>n</i>	Baseline nocturia	Mean reduction in nocturia (year 1)	Mean reduction in nocturia (year 4)	<i>N</i> ≥ 2 nocturia	Mean reduction in nocturia (year 1)	Mean reduction in nocturia (year 4)
Doxazosin	649	2.3	0.54*†	0.53*	484	0.77*†	0.77
Finasteride	653	2.4	0.40	0.42	496	0.60	0.68
Combination	653	2.3	0.58*†	0.55	487	0.80*†	0.79
Placebo	628	2.3	0.35	0.38	459	0.61	0.66

\*Statistically significantly different from placebo. †Statistically significantly different from finasteride.

However, although difficult to quantify, the authors stated that the reported changes in nocturia 'correlated with changes in the reported bother from nocturia', and they termed the effect 'moderate' on symptom-specific quality-of-life measures.

Another study analysed 3047 men from the Medical Therapy of Prostatic Symptoms (MTOPS) trial randomized to one of four groups: doxazosin, finasteride, combination therapy and placebo [6]. The outcome measured was the change in self-reported nocturia from baseline at a 1- and 4-year follow-up. The mean change in nocturia episodes are outline in Table 2. One would question the clinical significance of any of these results.

Another placebo-controlled study utilizing alfuzosin, showed a net advantage over placebo of 0.3 voids per night, statistically, but hardly clinically, significant [7] Some more recent studies have been reported to show more promising results with alpha-blockers, but these typically suffer from methodological considerations. One such study found that up to 95% of patients with LUTS suggestive of BPH had nocturnal polyuria, where nocturnal urine production exceeds one-third of the daily production [8]

They treated 20 such men with tamsulosin for 6 weeks and achieved a statistically significant reduction in nocturia episodes from baseline (3.3 to 2.4 episodes per night), but the study did not have a placebo arm. They did not show a significant reduction in nighttime urine production and do not suggest this as the mechanism of effect.

The best results reported with alpha adrenergic blockade are on a small patient sample (*n* = 59, excluding 'marked nighttime polyuria') in a multi-institutional study that compared a reduction in nocturia from baseline to 6 weeks with naftodopril and tamsulosin [9] Nocturia, as calculated from the IPSS nocturia score, decreased from 3.5 to 1.6 episodes per night with naftodopril and from 3.4 to 1.7 with tamsulosin, both significant results. No placebo group was included in this trial.

#### THERAPIES USED FOR THE MANAGEMENT OF OVERACTIVE BLADDER

Nocturia is commonly seen in the OAB symptom syndrome, and, when occurring more than one time per night, is one of the most bothersome symptoms. It is a common assumption that the first-line medications for OAB, antimuscarinics, exert a clinically

significant effect on this troublesome symptom of nocturnal awakening to void. The effect of solifenacin on male and female patients with OAB was assessed utilizing pooled data from four phase III randomized clinical trials [10] A total of 3032 patients were included in the analysis, with 2534 of these patients reporting nocturia at baseline. Sixty-two per cent of the patients reporting nocturia were classified as having nocturnal polyuria. In patients with nocturnal polyuria, the baseline number of nocturnal awakenings to void was higher (2.27–2.33) than those without nocturnal polyuria (1.66–1.70). Patients without nocturnal polyuria experienced a statistically significant reduction in nocturia, however, this translated to a numeric difference of only 0.18 episodes of nocturia less per night than placebo. In patients with nocturnal polyuria, no significant reductions in nocturnal episodes were noted.

In a double-blind placebo-controlled study which randomized 911 patients to 5 or 10 mg solifenacin or placebo for 12 weeks, a statistically significant reduction in nocturia by 0.71 episodes per night (vs 0.52 with placebo) was seen with the 10-mg dose [11] In the STAR (Solifenacin and Tolterodine as an Active comparator in a Randomized trial)

study, a secondary analysis showed that both solifenacin and tolterodine were statistically effective in reducing nocturia episodes from baseline (by 0.71 and 0.63 episodes per night, respectively), but there was no placebo [12]. In a double-blind placebo-controlled trial in patients flexibly dosed with solifenacin for 3 months, solifenacin improved urgency incontinence and frequency, but not nocturia [13]. The improvement with drug was 0.63 (baseline 1.7) and with placebo was 0.48 (baseline 1.6), a numerically similar but non-statistically significant result in this trial compared with the previous two. Previous studies that looked at the effects of fesoterodine on nocturia fail to show statistically significant or clinically significant changes for either nocturia or nocturnal urgency episodes [14,15]. Together, all of these studies can be interpreted as clinically insignificant.

A series of 131 women with at least one nightly episode of nocturia was reported as a subset analysis of 197 women with urge predominant incontinence [16]. The treatment arms were behavioural training with pelvic floor muscle exercises, drug therapy with oxybutynin 2.5 to 5 mg three times daily and placebo. The change in nocturia episodes for behavioural training was 1.9 to 1.4 episodes per night; for drug therapy 1.9 to 1.7 episodes per night; and for placebo 1.9 to 2.0 episodes per night. The median change of 0.5 episodes per night for behavioural training was statistically significantly better than drug therapy and placebo and amounted to 23.4% of behavioural training patients experiencing one less episode of nocturia per night (vs 4.3% of drug treated patients and 7.9% of placebo treated patients). Drug therapy was statistically better than placebo, but the clinical significance of this change is debatable.

A group of studies has been done with tolterodine which seem to characterize the spectrum of results seen with the antimuscarinic agents. The median percentage reduction in nocturnal micturition frequency with tolterodine, dividing the nocturnal voids into non-overactive bladder voids (no associated urgency), OAB voids (associated with urgency) and severe OAB voids (associated with severe urgency) showed no significant effect over placebo [17]. With nighttime medication dosing, there was a statistically significant improvement in OAB-related nocturnal voids, that is,

nighttime voids associated with urgency (30% reduction for drug and 22% reduction for placebo). For 'severe' OAB-associated nocturia, the reductions were 59% for drug and 43% for placebo, also statistically significant. However, when one looks at the absolute reductions in these studies, one realizes that it is hard to argue clinical significance, even in the statistically significant groups. These results do, however, suggest that antimuscarinics offer the most benefit to patients with significant urgency related nocturia and to those without nocturnal polyuria.

### COMBINED THERAPY

The results of two analyses that looked at combination therapy with an alpha-blocker and a 5ARI have been discussed previously [5,6]. A combination of tamsulosin and extended release tolterodine for the treatment of men with lower urinary tract symptoms and OAB showed a significant reduction in nocturia of 0.6 episodes per night (baseline 2.07), with a change in placebo, however, of nearly 0.4 (baseline 2.02) [18]. In a multi-modal treatment pilot study, men with a mean age of 67 years, all of whom had nocturia two or more times per night, received behavioural modification and, if qualified, one or more of the following drugs [19]. Those characterized as having BPH received terazosin, titrated to 10 mg. Those with daily frequency of eight or more times received tolterodine 2 mg immediate release twice daily or 4 mg extended release once daily. Those who took greater than 30 min to return to sleep after waking to void received 5 mg zaleplon, a non-benzodiazepine sedative/hypnotic. Seventy-five per cent of the studied patients received 1 drug, 20% 2 drugs and 5% no drugs. On a bladder diary, the mean nocturia episode change was 3.1 to 1.1, and on AUA symptom score tabulation 2.6 to 1.1. There was no placebo arm and there were no intra-group comparisons.

### OTHER STUDIES

The use of a non-steroidal anti-inflammatory drug, diclofenac, for patients with nocturnal polyuria has been reported in a small, 26 patients, placebo controlled crossover study [20]. The mean nocturnal frequency statistically decreased, but numerically improved only from 2.8 to 2.3 episodes per night. The placebo effect was much lower

than that generally seen, 2.8 to 2.7 episodes per night, perhaps owing to the pathophysiology. Nine patients (34.6%) improved greater than 0.5 episodes on this drug. In a somewhat unusual study, five self-administered sedatives or analgesics were compared in a blinded, randomized, parallel placebo-controlled trial [21]. The agents utilized were oxazepam (a short-acting benzodiazepine), naproxen (an anti-inflammatory), zopiclone (a non-benzodiazepine sedative), oxycodone (an opioid), trazadone (a sedative/antidepressant) and placebo. Each medication, blinded by a pharmacist, was taken 10 times for a total of 60 tests. The mean number of nocturia episodes for placebo was 1.6. Statistically significant differences were achieved with oxazepam (decreased to 0.6 episodes per night) and naproxen (decreased to 0.7 episodes per night). Out of a possible 10, four nocturia free nights were achieved with oxazepam and five with naproxen. Detailed metabolic records were kept and it was noted that oxazepam produced no change in urine volume whereas naproxen reduced water, salt and potassium excretion, reducing the volume of urine by 46%.

### DISCUSSION

Nocturia is associated with moderate bother, a diminution in HRQL and a detrimental impact on overall health. After careful analysis of the available literature on the treatment of this condition, a few important concepts become apparent when considering treatment success. Efficacious treatment should result in a clinically meaningful reduction in the number of nocturnal voiding episodes. This meaningful reduction is not necessarily the same as a statistically significant reduction as reported in scholarly articles, but rather, is a clinically significant reduction in nocturnal voids that actually matters to the patient. Additionally, the reduction in nocturnal voiding should also improve those conditions felt to be secondary to nocturia, such as falls, fractures, mood and HRQL. To date, there have been no nocturia trials assessing these secondary outcomes. Most studies look at 'success' only in terms of a statistically significant decrease in nocturia episodes with essentially no comment as to clinical significance or lack thereof. Few studies look specifically at other parameters which may be important, including sleep latency (time to first awakening) and total

daily sleep time, and fail to look at any correlation with HRQL or concomitant comorbidity.

Using simple logic, to decrease nocturia, a drug must do one, or a combination, of three things: (i) improve bladder emptying and thereby improve nocturnal bladder storage capacity; (ii) increase the volume at which bladder activity is elicited; or (iii) decrease the nocturnal production of urine. As available treatments for BPH address bladder emptying and treatments for OAB address threshold volumes for bladder activity, these drugs were likely targets to address nocturia. While neither of these categories of drugs has provided adequate clinical effect, the third potential mechanism, decreasing nocturnal urine production, has side effects and metabolic sequelae that require careful clinical monitoring. For that reason, most urologists continue to pursue the other agents despite marginal therapeutic impact.

Little success has been encountered with the use of 5ARIs in the treatment of nocturia in patients with BPH. With alpha adrenergic blockade there have been a few placebo controlled reports of statistically significant, but not clinically significant, decreases in nocturia and the same can be said for combination therapy with these two types of agents. Antimuscarinic agents have enjoyed the most notable statistical success in the reduction of nocturnal voids; however, the actual clinical impact of these reductions is questionable as we are often talking about a reduction of a half of a void, or less, per night. The only exception might be those patients with severe OAB and multiple episodes of urgency related awakening in which the mechanism of success has presumably more to do with the reduction in urgency than the true reduction in nocturia. Nevertheless, in the setting of OAB with associated nocturia and urgency, it is likely that these agents will continue to play a role in treatment. It is also likely, that additional therapies, with different mechanisms of action, will need to be implemented in order to accomplish a clinically significant reduction in nocturia.

#### CONFLICT OF INTEREST

Alan J. Wein is a paid consultant to Allergan, Astellas, Medtronic, Ferring, Novartis, Pfizer and Endo.

#### REFERENCES

- 1 **Staskin DR, Kelleher C, Bosch R *et al.*** Initial assessment of urinary and faecal incontinence in adult male and female patients. In Abrams P, Cardozo L, Khoury S, Wein AJ eds. *Incontinence*, 4th edn, Vol. 3. Paris: Health Publications Ltd, 2009: 331–412
- 2 **Asplund R.** Nocturia: consequences for sleep and daytime activities and associated risks. *Eur Urol* 2005; (Suppl.): 24
- 3 **Coyne KS, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E.** The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. *BJU Int* 2003; **92**: 948–54
- 4 **Speakman M.** Efficacy and safety of tamsulosin OCAS. *BJU Int* 2006; **98** (Suppl. 2): 13–7
- 5 **Johnson TM II, Jones K, Williford WO, Kutner MH, Issa MM, Lepor H.** Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the department of veterans affairs cooperative study trial. *J Urol* 2003; **170**: 145–8
- 6 **Johnson TM II, Burrows PK, Kusek JW *et al.*** The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. *J Urol* 2007; **178**: 2045–51
- 7 **Roehrborn CG, Van Kerrebroeck P, Nordling J.** Safety and efficacy of alfuzosin 10 mg once-daily in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a pooled analysis of three double-blind, placebo-controlled studies. *BJU Int* 2003; **92**: 257–61
- 8 **Koseoglu H, Aslan G, Ozdemir I, Esen A.** Nocturnal polyuria in patients with lower urinary tract symptoms and response to alpha-blocker therapy. *Urology* 2006; **67**: 1188–92
- 9 **Ukimura O, Kanazawa M, Fujihara A, Kamoi K, Okihara K, Miki T, Kyoto Prefectural University of Medicine Benign Prostatic Hypertrophy Research Group.** Naftopidil versus tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia with special reference to the storage symptom: a prospective randomized controlled study. *Int J Urol* 2008; **15**: 1049–54
- 10 **Brubaker L, FitzGerald MP.** Nocturnal polyuria and nocturia relief in patients treated with solifenacin for overactive bladder symptoms. *Int Urogynecol J Pelvic Floor Dysfunct* 2007; **18**: 737–41
- 11 **Cardozo L, Lisee M, Millard R *et al.*** Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol* 2004; **172**: 1919–24
- 12 **Chapple CR, Martinez-Garcia R, Selvaggi L *et al.*** A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR Trial. *Eur Urol* 2005; **48**: 464–70
- 13 **Vardy MD, Mitcheson HD, Samuels T-A *et al.*** Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT – a double-blind, placebo-controlled trial. *Int J Clin Pract* 2009; **63**: 1702–14
- 14 **Chapple C, Van Kerrebroeck P, Tubaro A *et al.*** Clinical efficacy, safety and tolerability of once daily fesoterodine in subjects with overactive bladder. *Eur Urol* 2007; **52**: 1204–12
- 15 **Dmochowski RR, Peters KM, Morrow JD *et al.*** Randomized, double-blind, placebo-controlled trial of flexible dose fesoterodine in subjects with overactive bladder. *Urology* 2010; **75**: 62–8
- 16 **Johnson TM II, Burgio KL, Redden DT, Wright KC, Goode PS.** Effects of behavioral and drug therapy on nocturia in older incontinent women. *J Am Geriatr Soc* 2005; **53**: 846–50
- 17 **Rackley R, Weiss JP, Rovner ES, Wang JT, Guan Z, O37 STUDY GROUP.** Nighttime dosing with tolterodine reduces bladder-related nocturnal micturitions in patients with overactive bladder and nocturia. *Urology* 2006; **67**: 731–6
- 18 **Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z.** Tolterodine and Tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder. A Randomized Controlled Trial. *JAMA* 2006; **296**: 2319–28
- 19 **Vaughan CP, Endeshaw Y, Nagamia Z, Ouslander JG, Johnson TM.** A multicomponent behavioural and drug intervention for nocturia in elderly men:

rationale and pilot results. *BJU Int* 2009; **104**: 69–74

- 20 **Addla SK, Adeyoju AB, Neilson D, O'Reilly P.** Diclofenac for treatment of nocturia caused by nocturnal polyuria: a prospective, randomised, double-blind, placebo-controlled crossover study. *Eur Urol* 2006; **49**: 720–5

- 21 **Kaye M.** Nocturia: a blinded, randomized, parallel placebo-controlled self-study of the effect of 5 different sedatives and analgesics. *Can Urol Assoc J* 2008; **2**: 604–8

**Correspondence:** Ariana L. Smith, Division of Urology, Hospital of University of

Pennsylvania, 3400 Spruce Street, 9 Penn Tower, Philadelphia, PA 19104, USA.  
e-mail: alan.wein@uphs.upenn.edu

**Abbreviations:** **5ARI**, 5-alpha reductase inhibitors; **HRQL**, health-related quality of life; **OAB**, overactive bladder; **MTOPS**, Medical Therapy of Prostatic Symptoms.