Nocturia is a disease of multifactorial etiology affecting both men and women. The purpose of this article is to review the outcome of clinical trials for treatment of nocturia. Therapy of nocturia due to nocturnal polyuria includes timed diuretics, positive airway pressure and desmopressin where clinically indicated. Patients with nocturia due to bladder storage problems have been treated with anticholinergics resulting in little demonstrable overall benefit, although such investigations have not been powered to determine the effect of this class of medications specifically in patients with nocturnal urgency. Therapy for nocturia owing to benign prostatic hyperplasia includes $\alpha$-blockers and $5\alpha$-reductase inhibitors, with variable outcomes. Future treatment for nocturia mandates well-designed clinical trials to determine the efficacy of cause-specific approaches.

Keywords: $\alpha$-blockers • anticholinergics • benign prostatic hyperplasia • desmopressin • nocturia • nocturnal polyuria • nocturnal urgency

According to the International Collage of Surgeons’ 2002 definition, nocturia is waking up at least once or more during the night to void. This definition further identifies night-time as the period of time during which the intent is to sleep without waking unless to purposely arise [1]. Nocturia is common for both men and women of all ages – younger women have higher prevalence than younger men (20.4–43.9% and 11–35.2%, respectively) and older men have higher prevalence than older women (69–93% and 74.1–77.1%, respectively) [2]. Nocturia of two or more voids has a diminishing effect on health-related quality of life and three or more voids is associated with moderate or major bother [3]. Among the elderly, nocturia is a risk factor for falls and increased mortality [4,5].

Nocturia is a multifactorial condition that could result from many causes (Box 1) and its etiology remains under investigation. Nocturia is often considered to be a storage component of lower urinary tract symptoms (LUTS) and yet is often clinically treated as being secondary to benign prostatic hyperplasia (BPH) in men or overactive bladder (OAB) in women. By way of example, polyuria may cause urinary frequency in the absence of a urological condition and may be due to problems with fluid handling by the kidneys or related to cardiovascular dysfunction, as well as a whole host of other conditions [6]. It is suspected that treatment of nocturia will be most effective if the correct pathology is targeted. Accordingly, we aim to outline in this review the outcomes of cause-specific therapy of nocturia.

Nocturia may be characterized as arising from some combination of the following four categories: nocturnal polyuria (NP), reduced nocturnal or 24-h bladder capacity, mixed (combination of NP and low capacity) and 24-h polyuria. In order to quantitate the changes in these symptoms as a function of age, sex and treatment, several indices derived from the frequency volume chart may be utilized [7]. The nocturia index (Ni) is calculated by: nocturnal urine volume (NUV) divided by maximum voided volume. If Ni >1, then nocturia results from nocturnal production of urine in excess of bladder capacity. An example illustrating this point would be a person who voids...
Box 1. Main causes of nocturia and definitions.

- 24-h polyuria: 24-h urine production >40 ml/kg
- Nocturnal polyuria: nocturnal voided volume >20% of 24-h volume for the young; >33% for the elderly
- Decreased bladder capacity: FVC-derived determinant NBCi >2 and Ni >1; less discriminatory for elderly
- Mixed (NP and decreased bladder capacity): NP, decreased bladder capacity; possible sleep disturbance

FVC: Frequency volume chart; NBCi: Nocturnal bladder capacity index; Ni: Nocturia index; NP: Nocturnal polyuria.

700 ml of urine during the night however, his maximal voided volume is 350 ml, suggesting that the patient will be obligated to rise out of bed to avoid incontinence. Ni values increase significantly with age in both sexes [8].

The NP index (NPI) is defined as NUV divided by 24-h urine volume. Patients with an NPI of >33% have NP at any age [1]. NPI values also increase significantly with age regardless of sex [8]. The nocturnal bladder capacity index is calculated as the difference between actual number of nightly voids and predicted number of nightly voids (Ni-1). Unlike Ni and NPI, which both increase with age, the nocturnal bladder capacity index decreases significantly with age in both men and women, suggesting that decreased bladder capacity is relatively less important than NP in the overall etiology of nocturia in elderly patients [8].

Polyuria is defined as a 24-h urine production of more than 40 ml/kg (2800 ml in a person weighing 70 kg) [1]. When the voided volume of urine at night is >20% of 24-h volume in the young and 33% in the elderly, the etiology of nocturia is due to NP.

According to a 2009 study exploring factors contributing to nocturia, NP was the predominant cause in 33% of the patients (133 women, 191 men) with a mean age of 63 with nocturia [9]. Nocturnal polyuria has been found to be the most prevalent factor in predicting nocturia in almost 90% of patients diagnosed with nocturia [5]. One mechanism that has been explored to explain NP is reabsorption of third spaced fluid, which accumulates during the day, especially in patients with congestive heart failure and/or venous lower extremity disease. A correlation between the relationship of accumulated extracellular fluid in the legs from 8am to 9pm and the NUV voided from 10 pm to 6 am was reported to confirm the conversion of extracellular fluid into nocturnal urine output [10]. This pathophysiology might be a cause of low diurnal production of urine and may be treated with timed (mid-afternoon) diuretics or with preventative use of mildly compressive lower extremity stockings.

The use of timed diuretic administration was explored in a study in which an afternoon dose of furosemide 40 mg was administered to elderly men presenting with LUTS. This placebo-controlled trial showed that patients with NP had a significant reduction in nocturnal frequency and NUV as a result of the active medication [11]. This study was preceded by one in which bumetanide, a loop diuretic, was used to treat patients with heart failure and those unresponsive to furosemide. Although a small study, bumetanide treatment significantly decreased the weekly number of nocturia episodes and 11 patients preferred active medication to placebo [12]. It remains unclear what benefit loop diuretics confer upon patients with nocturia due to NP, but it does seem to offer some advantage over placebo and can be utilized as empirical treatment.

Another strategy for patients with NP is to provide an antidiuretic at bedtime to defer excessive urine production until waking hours. The only medication in this class approved for treatment of nocturia worldwide is desmopressin, a synthetic analogue of arginine vasopressin. Desmopressin has a greater antidiuretic effect than arginine vasopressin, but has poor affinity for vasopressin receptors on blood vessels and therefore has little vasopressor effect [13]. The antidiuretic effects of desmopressin significantly increase urine osmolality and in turn have been shown to decrease NUV, as well as nocturnal frequency of voids, with little change in sodium excretion [14]. It remains unclear whether the efficacy of desmopressin in reducing NUV is independent of deficiency in endogenous arginine vasopressin release [15].

The efficacy of desmopressin has been demonstrated in treating nocturia due to NP in a small placebo-controlled study of 17 patients with a mean age of 68 years. The improvement in nocturnal diuresis and frequency of voids was seen over a 2-week period, during which desmopressin was administered at bedtime [16]. Whether desmopressin treatment provided a clinical response, defined as a decrease by more than 50% of mean baseline nocturnal voids, was subsequently addressed in a randomized, double-blind, placebo-controlled study. In 151 male patients diagnosed with nocturia due to NP (mean age 65 years) a reduction in baseline mean nightly voids by >50% was used as the primary outcome. The 3-week trial of desmopressin decreased nightly voids by half in 34% of the men versus 3% given placebo [17]. A similar 3-week trial of desmopressin versus placebo also reported beneficial outcomes in women (mean age 55 years) diagnosed with nocturia (≥two voids/night) [18]. The efficacy of desmopressin in producing a meaningful clinical response was further demonstrated in both men and women during...
long-term trials of 10–12 months, with improvements not only in nocturnal frequency and diuresis, but also in quality of sleep [19–22]. Although desmopressin has been found to be an effective treatment for nocturia in both men and women, there have been reports of significant gender differences in response to desmopressin. Women over 50 years of age are more sensitive than men to the effects of desmopressin upon reducing both NUV and serum sodium levels over a 4-week period [23]. This difference was explained, at least in part, by the finding of higher plasma concentrations of desmopressin in women than in men. Although the study was small (24 patients), the increased plasma concentration suggests a longer lasting effect experienced by female patients than male patients and should be taken into account when selecting a therapeutic dose for elderly women [24].

Nocturia patients who do not exhibit signs of NP may have bladder storage problems during the night. Bladder capacity may be reduced as a result of a host of urological conditions ranging from bladder outlet obstruction, nocturnal detrusor overactivity, radiation cystitis, urinary calculi and pharmacologic agents, such as β-blockers, consumed close to bedtime [25].

Nocturia as a result of bladder storage problems has been the focus of studies of clinical trials utilizing anti-Cholinergic medications. In a 12-week randomized, placebo-controlled study, 850 patients (mean age 60 years) were administered tolterodine extended release (TER) or a placebo before bedtime if they suffered from OAB (≥8 voids/24h) and nocturia (>2.5 voids/sleep cycle). While there was no overall benefit in terms of nocturia response to TER versus placebo, TER was shown to significantly reduce OAB-related and severe OAB-related nocturnal micturitions versus placebo [26]. A post hoc analysis was performed of the 12-week trial described above to evaluate the efficacy of TER in nocturia patients having OAB without incontinence as predicted by completion of a 7-day voiding diary at baseline. This analysis, which included 513 patients, 58% male (mean age 58 years) who had continent OAB and nocturia at baseline, reported similar effects of TER treatment in reducing severe OAB-related night-time voids per week compared with placebo (p < 0.05) [27].

A different post hoc analysis was performed in men comparing two similar 12-week studies testing the efficacy of TER in patients with OAB and nocturia. This subanalysis included 745 men (mean age 64 years) who were mostly continent (27% reported incontinence according to the 7-day voiding diary at baseline) and who had a mean of 13 voids per 24 h and 3.5 voids per night. Efficacy of TER versus placebo was reported as the median percentage change in the number of voids from baseline to week 12. Significant reductions of severe OAB-related night-time voids were reported in the TER-treated group (-77.8% median change) versus placebo (-50% median change). Mean reduction in urgency rating (1–5) for each micturition as recorded in the 7-day voiding diary was greater for the TER-treated group during the night-time (-0.17), daytime (-0.09) and 24-h intervals (-0.12) versus placebo (-0.03, -0.02 and -0.03, respectively) [28].

Solifenacin has been studied with regard to its effects on nocturia in a cohort of patients with OAB. In a retrospective analysis of four Phase III clinical trials of solifenacin treatment in such patients, the efficacy of solifenacin was evaluated with regard to reduction of nocturia frequency as a function of the presence or absence of NP. This analysis showed that solifenacin versus placebo significantly reduced nocturnal voiding episodes in patients without NP, which was not the case for the cohort of patients with NP (defining NP as greater than the 33% cut point) [29]. However, examination of the data reveals that the placebo performed considerably better in patients with NP than in those without NP, accounting for the apparent lack of efficacy in the former group. In larger studies of solifenacin examining its efficacy in treating OAB symptoms, solifenacin demonstrated little benefit in improving nocturia [30,31]. A recent post hoc analysis of a 12-week Phase III trial of solifenacin 5 and 10 mg versus placebo in treatment of OAB included 962 patients (82% female) with a minimum of one night-time void (mean of two voids/night) at baseline and completed a 3-day voiding diary prior to follow-up visits. This analysis reported nocturia reduction of 0.42 and 0.46 by solifenacin 5 and 10 mg, respectively, versus 0.34 by placebo, with the reduction of 10 mg by solifenacin being statistically significant [32]. However, it can be argued that an improvement of 0.12 episodes of nocturia by drug net of placebo is hardly clinically relevant.

There has been substantial research in studying the efficacy of α-blockers in treatment of LUTS secondary to BPH. Some α-blockers such as tamsulosin, terazosin, doxazosin and alfuzosin are indicated in the 2010 AUA Update of Clinical Guidelines on BPH as appropriate medical therapy in treating LUTS secondary to BPH [33]. Silodosin, a selective α1a adrenoreceptor blocker, was tested in a large, randomized, placebo-controlled study as a comparable alternative to tamsulosin in treatment of LUTS secondary to BPH, as measured by change from baseline in total International Prostate Symptom Score (IPSS). Of the 955 men ≥60 years of age who had LUTS (IPSS ≥13) and bladder outlet obstruction (uroflow 4–15 ml/s, minimal voided volume for uroflow being 125 ml), 764 reported nocturia at baseline and were included in the subanalysis of silodosin effect in regard to nocturia episodes as compared with tamsulosin and placebo. In this subgroup, silodosin and tamsulosin reduced
Naftopidil is an α-blocker that has both voiding and storage effects on treatment of men with LUTS related to BPH. In rodent studies, naftopidil has been shown to have affinity for both α-1a and -1d adrenoceptors [35]. Using the frequency volume charts and IPSS scores as outcome measures, 81 men with BPH (mean age 69 years) and LUTS who were treated with naftopidil for 6 weeks showed an improvement in LUTS: total IPSS score decreased from 19.1 ± 6 to 10.5 ± 6.5. Of the 81 men, 40 had nocturia (mean 3.2 voids/night) at baseline, which was reduced by naftopidil to 2.3 voids/night (p < 0.0001) [36]. The lack of placebo in this study greatly diminishes its interpretability. In an exploratory, nonplacebo-controlled study, 122 men with BPH/LUTS including ≥3 night-time voids and who had failed improvement on tamsulosin (nocturia -0.2) were treated with naftopidil for 6 weeks following washout, with placebo crossover. Naftopidil reduced nocturia from 3.1 ± 0.6 to 1.2 ± 0.8 and the voiding and storage symptom scores of the IPSS from baseline of 7.7 ± 3.5 and 5.4 ± 3 to 2.7 ± 2 and 2 ± 1.8, respectively [37]. When comparing the efficacy of tamsulosin (n = 28) and naftopidil (n = 31) in men with BPH/LUTS (mean age 69 years), both treatments produced comparable improvements in nocturia frequency (-1.7 and -1.9, respectively) [38]. Naftopidil had similar clinical efficacy as tamsulosin in treatment of LUTS secondary BPH when compared in crossover design, however, due to lack of randomized, placebo-controlled data, their therapeutic effects with regard to improvement in nocturia are questionable [39,40].

BPH-related obstructive uropathy is often treated with 5α-reductase inhibitors, either alone or in combination with α-blockers. A post hoc analysis was performed using data from the VA Cooperative Study Program Trial in which 1229 elderly men with BPH were given terazosin and/or finasteride versus placebo to evaluate whether terazosin alone or in combination with finasteride reduced nocturia, the latter found in 1040 of these men. The secondary analysis included 788 men (nocturia ≥2 at baseline) who completed 12 months of treatment, showing that nocturnal voids were reduced by half in 39% of patients treated with terazosin (n = 199), in 25% treated with finasteride (n = 205), in 32% treated with combination therapy (n = 195) and in 22% for placebo (n = 189) [41]. Statistical differences amongst these subgroups were not carried out. A similar analysis of another multicenter study, MTOPS, evaluated the efficacy of doxazosin alone or in combination with finasteride in reducing nocturia in men using a change in self-reported nocturia from baseline as the primary outcome. The subanalysis, which included 1926 BPH men with nocturia ≥2 at baseline (mean age 63.2 years) showed that both doxazosin and a combination of doxazosin plus finasteride reduced nocturia by 0.77 and 0.80, respectively, from baseline after 1 year, and by 0.77 and 0.79, respectively, after 4 years of treatment. These changes were significant only at 1 year, presumably due to drop-off in numbers of patients evaluable in the long-term study. Finasteride versus placebo reduced nocturia by 0.60 and 0.61 from baseline after 1 year, respectively, and by 0.68 and 0.66 from baseline after 4 years, respectively. The reduction in nocturia by finasteride versus placebo was not significant at either 1 or 4 years [42].

Several groups have investigated the role of nonsteroidal anti-inflammatory drugs (NSAIDs) such as loxoprofen as an alternative medical therapy in treatment of nocturia. In a nonplacebo-controlled study of 93 men (mean age 70 years, baseline of ≥2 voids/night) receiving α-blockers, nocturia was evaluated based on the response to the IPSS nocturia question before and after loxoprofen treatment as excellent or having disappeared (decrease of ≥2 voids/night), improved (decrease of one void/night), or unchanged or worsened (no decrease/increase of voids/night). After 2 weeks of loxoprofen treatment, nocturia decreased by ≥2 voids/night in 37.6% of patients and decreased by one void/night in 36.6%, with an overall excellent/improved response in 74.2% [43].

Another NSAID, celecoxib, was studied in a randomized, placebo-controlled study of 80 men (mean age 64.3 years) with nocturia ≥2 using the IPSS question 7 score as a primary outcome measure. After 1 month of treatment, celecoxib decreased nocturia from 5.17 ± 2.1 to 2.5 ± 1.9 (p < 0.0001) versus placebo reduction from 5.30 ± 2.4 to 5.12 ± 1.9 [44]. The mechanism by which NSAIDs effectively treat nocturia is proposed to be by decreasing NUV and increasing bladder capacity [45,46].

Although nocturia is generally considered to be a urological problem, it causes sleep degradation and therefore may be classified as a sleep disorder. Acute sleep deprivation was studied in 20 healthy adults (ten female, mean age 25 years) to test if a change from the normal circadian rhythm in NUV occurs and if physiologic handling of water and solutes is affected. Every patient underwent two 24-h sleep studies, one with sleep and one with no sleep, the order of which was randomized. At baseline, women were found to have higher urine osmolality during the night (467 ± 57 mosmol/kgH2O) than men (364 ± 30 mosmol/kgH2O) and lower osmolality during the day (362 ± 30 mosmol/kgH2O) than men (464 ± 69 mosmol/kgH2O). Sleep deprivation increased the mean nocturnal diuresis from 1.01 ± 0.06 to 1.61 ± 0.13 ml/kg-h and decreased urine osmolality from 416 ± 32 to 366 ± 15 mosmol/kgH2O. Men had higher nocturnal diuresis (1.82 ± 0.22 ml/kg-h) than women (1.41 ± 0.11 ml/kg-h).
kg·h) as a result of sleep deprivation (p < 0.01). The mechanism of action that may explain this observation is impaired circadian regulation of the renin–angiotensin–aldosterone system [47]. More recently there has been the demonstration of increased sensitivity to the effects of circulating antidiuretic hormone in woman as compared with men [23].

Two studies explored the effects of melatonin on nocturia. In a crossover, placebo-controlled study of 20 men (mean age 72.2 years) with prostatic enlargement and self-reported nocturia (≥three voids/night), melatonin or placebo was randomly administered for a 4-week period with crossover treatment following a 7-day washout period. Nocturia reduction from baseline, as recorded in the frequency volume chart, was not significant by either treatment (melatonin: -0.3; placebo: -0.1), nor was it significant as reported by question 7 of IPSS (melatonin: -0.5; placebo: 0) [48]. When comparing melatonin to a hypnotic, 42 patients (25 men) with nocturia >2, randomized to receive melatonin (20) versus rima1zafone (22) showed significant reduction of self-reported nocturnal voids from baseline in both treatment groups (-0.8 and -0.10, respectively) [49]. The latter study should be interpreted with caution owing to both small size and the absence of a placebo arm.

In a prospective study, 97 patients (75 men; mean age 55 years) with obstructive sleep apnea (OSA) and nocturia were treated with continuous positive airway pressure (CPAP) for at least 1 month. CPAP treatment produced a statistically significant change in two baseline parameters for nocturia: self-report during 1 week at home (from 2.5 ± 2.4 voids/night to 0.7 ± 0.6 voids/night) and self-report during one diagnostic night in the laboratory (from 1.1 ± 0.9 voids/night to 0.5 ± 0.6; p < 0.0001). When comparing patients with mild/moderate OSA (n = 50) versus severe OSA (n = 47), patients with severe OSA had worse nocturia and experienced a greater reduction in nocturia after CPAP treatment, although CPAP significantly improved nocturia in both groups, (p < 0.001) [50]. The pathogenesis of nocturia in OSA has been demonstrated to be mediated by hypoxemia causing pulmonary vascular constriction and secondary increase in right atrial pressure, resulting in increased cardiac secretion of atrial natriuretic peptide [51].

Future perspective

Future investigation of the condition of nocturia merit an evaluation of the value of commonly utilized diagnostic tools such as frequency-volume charts and nocturia-specific questionnaires in elucidating the etiology of nocturia guiding the choice of treatment options. Description of nocturia and related symptoms, including urgency grades for each nocturnal void as well as quality of sleep, will allow for a better understanding of the foundations of how nocturia interferes with overall quality and quantity of life. A simple comparison of the number of hours slept per night and nocturia severity needs to be carried out. Assessment of the various stages of sleep in nocturia patients utilizing polysomnography may provide additional insight into the effect of nocturia upon sleep quality and the latter’s response to therapeutic intervention.

Future outcome trials of nocturia therapy may include relevant end points, including severity of nocturia, quantitation of nocturnal urgency perception grade and the impact of nocturia on quality of sleep, health-related quality of life, cognitive function, morbidity and mortality. Additional research is warranted assessing the outcomes of available therapies for nocturia, including behaviour modification, timed diuretics/antidiuretics and antimuscarinics. Epidemiological investigations of the impact of nocturia amongst populations of varying age, socioeconomic and racial composition, in addition to the overall economic burden and cost–effectiveness of nocturia therapy within our society merit considerable attention.

Executive summary

- Evaluation and classification of the etiology of nocturia is best facilitated by analysis of the 24-h frequency volume chart (voiding diary).
- Nocturnal polyuria has many underlying medical causes that provide a wide array of opportunities for effective therapy of nocturia.
- Therapy of nocturia using anticholinergics demonstrates a consistent pattern of statistically significant, but clinically insignificant benefit, suggesting that future research should address nocturnal urgency as being more relevant to the mechanism of action of this class of uropharmaceuticals as currently understood.
- Therapy of nocturia using medications treating benign prostatic hyperplasia alone or in combination, as in the case for anticholinergics, demonstrates at best only clinically marginal benefit.
- Nonsteroidal anti-inflammatory drugs have demonstrated some efficacy in treating nocturia by mechanisms that have been poorly studied and deserve investigation in the future with more robust clinical trial designs.
- Among all known individual treatments for nocturia, identification of obstructive sleep apnea followed by cause-specific therapy with continuous positive airway pressure has shown the greatest benefit to date for night-time voiding.
Financial & competing interests disclosure

JP Weiss has consulted for Ferring, Pfizer, Astellas and Allergan. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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References

Papers of special note have been highlighted as:

■ of interest

■■ of considerable interest


■■ Evaluation of nocturia using the frequency volume chart derived parameters was demonstrated to be instrumental in choosing appropriate treatment.


■ Additional research investigating effectiveness of timed diuretics is warranted due to the paucity of data illustrating the benefit of treatment.


■ Desmopressin was shown to be the gold standard in treatment of nocturia due to nocturnal polyuria, and also has an effect on prolonging sleep.


■■ Further research of gender differences in response to desmopressin treatment may elucidate a pathophysiology more specific to women than men, which has not been previously investigated.


Assessing nocturia in clinical trials

Clinical Trial Perspective


Additional research of clinical outcomes of nonsteroidal anti-inflammatory drugs in treatment of nocturia may be useful in developing a treatment regimen with minimal adverse events than current therapeutics in use.


Nocturia due to sleep apnea is effectively treated by continuous positive airway pressure, therefore obstructive sleep apnea should be included in the differential diagnosis of nocturia.
