World Journal of Urology (2019) 37:1389–1394
https://doi.org/10.1007/s00345-018-2511-4

ORIGINAL ARTICLE

Diagnosis and management of nocturia in current clinical practice: who are nocturia patients, and how do we treat them?

Siri Drangsholt[1] · Maria Juliana Arcila Ruiz[2] · Benoit Peyronnet[3] · Nirit Rosenblum[2] · Victor Nitti[2] · Benjamin Brucker[2]

Received: 31 July 2018 / Accepted: 24 September 2018 / Published online: 4 October 2018

Abstract

Objective To characterize the current evaluation, and efficacy of treatments in patients with the primary complaint of nocturia.

Methods A retrospective chart review was performed of new patient encounters seen in a tertiary urology practice from May 2010 to September 2016 with the primary diagnosis of nocturia (ICD-9 788.43 and ICD-10 R35.1).

Results 595 patients were identified. 403 met inclusion criteria. The median patient reported that nocturia episodes were 4 (1–20). 192 patients (48%) reported previous treatment for nocturia. After the index visit, a bladder diary (BD) was utilized in 50% of patients, with a 62% ($n=124$) completion rate at follow-up visit. On BD analysis, the most common etiologies of nocturia were nocturnal polyuria 76% ($n=90$) and overactive bladder in 21% ($n=26$). Patient reported improvement with therapy after BD completion was 46% ($n=34$), similar to patients without voiding diaries (43% improvement, $n=153$). Anticholinergics and alpha blockers were the most commonly recommended drug, but no specific medication was associated with nocturia improvement. Oral desmopressin was used in 5% of patients.

Conclusion Nocturia is a common condition and very commonly patients have sought treatment prior to presentation. Bladder diaries were recommended to half of the patients. Patient reported that improvement did not seem to correlate with completion of a bladder diary. Though most patients had NP the use of desmopressin was very low. Current treatments used in managing nocturia may lack efficacy.

Keywords Nocturia · Frequency volume chart · Desmopressin · Nocturnal polyuria

Introduction

Nocturia is a condition that interrupts sleep secondary to waking at night to void. A meta-analysis by Cornu et al. [1] reported a 30% incidence in men and women age 60–69 who void ≥2 times a night and a 73% incidence who void ≥1 at night. Nocturia negatively impacts quality of life and contributes to impaired sleep and overall health [2, 3]. It is the leading cause of sleep disturbance in patients older than 50, places elderly patients at risk of falling, and is associated with increased mortality [4]. Several urological and non-urological causes of nocturia exist. In some instances, nocturia can be due to a single etiology, but often times it is multifactorial. We can consider causes of global overproduction of urine, isolated overproduction of nighttime urine [i.e., nocturnal polyuria (NP)], decreased functional bladder capacity, and primary sleep disturbances [5, 6]. Until very recently, in the United States, there has been no medication approved specifically to treat nocturia. Clinicians have often relied on medication that are primarily used for other conditions such as BPH (Benign Prostatic Hypertrophy) or OAB (Overactive Bladder) [7–9]. These medications may treat bladder over activity and bladder emptying problems but do not treat issues with excessive urine production. Desmopressin, an analog of arginine vasopressin, treats excessive urine

✉ Siri Drangsholt
siri.drangsholt@nyumc.org

[1] Department of Urology, New York University School of Medicine, 222 E 41st St 11th Floor, New York 10017, NY, USA

[2] Division of Female Pelvic Medicine and Reconstructive Surgery, New York University Langone Health, 222 E 41st St 11th Floor, New York 10017, NY, USA

[3] Department of Urology, Service D'Urologie, University of Rennes, 2 Rue Henri Le Guilloux, 35000 Rennes, France

production by increasing renal fluid reabsorption leading to more concentrated urine production. Despite being available for years, it has not been widely used in adults. This is likely because of lack of approval, unpredictable pharmokenetics, fear of associated side effects and overall modest efficacy [10]. Recent FDA approval of new medications to treat nocturia may influence this treatment paradigm.

Currently, treating physicians largely rely on history to direct treatment strategy. The bladder diary (BD) or frequency volume chart (FVC) is the test of choice to determine the etiology of nocturia and has been used by researchers and clinicians [5]. BD can suggest the pathological process and help narrow the myriad etiologies and, in some cases, treatments. However, diaries can be labor intensive and result in variable compliance [11]. Furthermore, adherence with medications for nocturia is poor and thus improvement is somewhat limited [12].

The current project seeks to review the current treatment patterns of patients that are seen for nocturia in a high-volume tertiary urologic center. We report the evaluation experience of patients presenting with nocturia and review outcomes based on available therapies. The results will help understand this population and identify practice patterns, or treatments, aiming to provide meaningful improvement in nocturia. Specifically, who are patients that seek treatment with specialized urologists, are we following the recommended practice of diaries and do these measures improve nocturia.

Materials and methods

A retrospective chart review of all new patient encounters seen in a functional urology practice with the diagnosis of nocturia. An electronic medical record, implemented in 2010, was queried from May 2010 to September 2016 for patients with a primary diagnosis of nocturia with ICD-9 788.43 and ICD-10 R35.1 codes. All patients were evaluated and treated by one of three female pelvic medicine and reconstructive surgery certified urologists (FPMRS). Up to three visits within a 12-month period from the time of presenting were reviewed. Inclusion criterion was a primary diagnosis of nocturia, patients were excluded if they had undergone a treatment for prostate cancer or bladder cancer, had a history of recurrent UTIs or had OAB predominant daytime symptoms. This was determined by two reviewers (SD, MR) and if there was a discrepancy a third reviewed (BB) and determined if OAB was the predominant complaint. Patients who had OAB symptoms (i.e., urgency, frequency, urgency incontinence), but it was determined by review that nocturia was the primary complaint, were included. Patient-specific characteristics including nocturia episodes, coronary artery disease, primary sleep disorder, diabetes, obesity, body mass index (BMI), diuretic use and prior lower urinary tract medications were collected from initial visit. Recommended treatments were categorized to behavioral treatment (fluid restriction, bladder irritant reduction, physical therapy, leg elevation, compressive stocking, etc.), alpha-blockers, anticholinergics, B3 agonists, desmopressin, timed diuretic use, third line overactive bladder (OAB) treatments (onabotulinum toxinA, percutaneous tibial nerve stimulation, interstim) and surgery. Behavioral treatments were offered to all patients as first line if they had not implemented these maneuvers prior to presentation. Outcome was determined by patient-reported improvement and change in nocturia events. Patient-reported improvement was based on the review of clinical records by two reviewers (SD, MR) and if there was a discrepancy in this determination a third reviewed (BB) and would decide if the patients response was considered an improvement. Patient self-reported nocturic episode events were used to calculate change in nocturic episodes. Only complete records were included in the analysis of BD data. BD outcomes obtained were: daytime voids, nighttime voids, 24-hour fluid intake and output, maximal voided volume, and 24 h nocturnal polyuria index score (NPI). Interpretation of BD results was categorized into the following categories: polyuria, nocturnal polyuria and bladder storage problems/OAB, and combination of diagnosis. BDs were analyzed according to provider interpretation and retrospectively using ICS definitions [5]. NP was defined as NPI ≥ 0.33 for age ≥ 35 and NPI ≥ 0.20 for age < 35 [5]. Univariate analysis was performed using nonparametric independent tests, Chi-squared analysis, and Pearsons correlation using IBM® SPSS® software. A two-sided $p < 0.05$ indicated statistical significance.

Results

595 patients were identified and 192 patients were excluded, 403 met inclusion criteria and were a new patient evaluation during the study period. Patients were excluded on the basis of treatment for bladder or prostate cancer, recurrent UTIs or OAB predominant symptoms. Of these, 239 (59%) were female, average age was 71 years (21–97) old and mean BMI was 25.6 (14–54). The median nocturia episodes were 4 (1–20); 254 (63%) patients had comorbidities, most frequently a cardiac history in 100 (25%), followed by obesity in 34 (8.4%) (Table 1). For patients who completed three visits, the mean nocturia events from the first visit improved from 4.1 to 2.96 episodes per night by the third visit ($p = 0.007$). Older age, BMI, history of sleep disorder, constipation, prior treatment and multiple comorbidities were all associated with higher baseline nocturia events ($p = 0.01$, $p = 0.05$, $p = 0.001$, $p = 0.02$ and $p = 0.007$, $p = 0.009$, respectively).

Table 1 Patient characteristics and treatments

Total patients	403
Female	239 (59%)
Mean age	71 (21–97)
Mean BMI	25.6 (14–54)
Meadian number of nocturia episodes	4 (1–20)
Comorbidities	254 (63%)
None	150 (37%)
Cardiac history	100 (25%)
Obesity	34 (8%)
Diabetes	14 (4%)
Sleep disorder	12 (3%)
Constipation	20 (5%)
Other	21 (5%)
Two or more	52 (13%)
Patients prior treatment type	192 (48%)
Alpha blocker	79 (19.6%)
Anticholinergic	108 (26.8%)
B3 agonist	17 (4.2%)
Follow-up visit #1	292 (65%)
Initiated treatment	204 (70%)
Reported improvement	117 (40%)
Follow-up visit #2	193 (48%)
Initiated treatment	170 (88%)
Reported improvement	88 (46%)

One-hundred and ninety-two patients (48%) reported previous treatment for nocturia, most commonly with anticholinergics (56%) and α-blockers (41%). Prior treatment was not associated with nocturia improvement ($p = 0.498$). Of all comorbidities evaluated (diabetes, obesity, asthma, coronary artery disease, diuretics, sleep disorder, BMI, age), only patients with a history of constipation were associated with nocturia improvement ($p = 0.01$).

After the index visit, a frequency volume chart bladder diary (BD) was recommended to 50% of patients ($n = 199$), with 62% ($n = 124$) of these patients complying. Based on univariate analysis, provider was associated with the likelihood of BD recommendation ($p < 0.001$). No specific provider was associated with change in nocturia number ($p = 0.076$). Of patients who completed BD, the most common etiologies of nocturia were nocturnal polyuria in 76% ($n = 90$) and overactive bladder/reduced bladder capacity in 21% ($n = 26$). Patient-reported improvement with therapy after FVC completion was 46%, similar to improvement in patients without BD (43%, $p = 0.323$). Nocturia improvement was not associated with the completion of bladder diary ($p = 0.310$). Higher nocturnal polyuria scores were found to be a factor associated with improvement in nocturia number ($r = 0.326$, $n = 124$, $p = 0.01$), but this was not correlated with any particular therapy, including desmopressin.

At the first encounter, in addition to behavioral therapies, additional intervention was suggested in 25% of patients. Of the entire group, 65% ($n = 292$) of patients returned for second visit at a mean of 16 weeks. Of these patients, 70% ($n = 204$) were compliant with the recommended treatment and 40% ($n = 117$) reported improvement. 48% ($n = 193$) of the original patients returned for a third visit. By the third follow-up, 88% ($n = 170$) had initiated intervention beyond conservative therapy (i.e., pharmacologic agents, third line treatments for OAB or surgery for other conditions) with only 46% ($n = 88$) reporting improvement (Fig. 1).

Initiation of non-behavioral treatment alone was not associated with change in nocturia episodes at second ($p = 0.090$) or third visit ($p = 0.701$). A third visit was associated with patient-reported improvement ($U = 7175$, $z = -2.672$, $p = 0.008$). Only 5% of all patients ($n = 22$) were recommended treatment with desmopressin (Fig. 2). Of these patients, 77% ($n = 17$) had an BD documenting nocturnal polyuria.

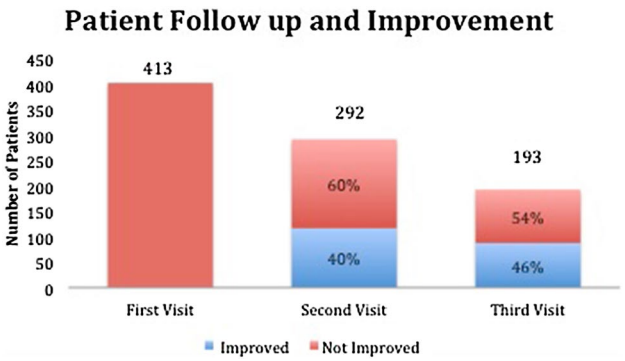

Fig. 1 Patient follow up and reported improvement

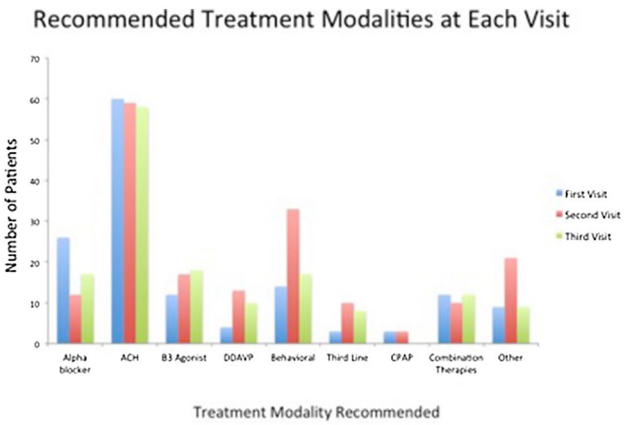

Fig. 2 Frequency of suggested treatment modalities by patient visit number

Discussion

Nocturia is a common condition that equally affects men and women of all ages with increasing prevalence in older populations. The International Continence Society (ICS) defines nocturia as the complaint to wake to void one or more times a night [5], although evidence suggests that ≥ 2 voids night are more likely to negatively impact an individual [3]. This correlates with the current study where it was found that 93% of patients reported ≥ 2 voids a night. It has previously been reported that patients often wait an average of 92 weeks from symptom onset to evaluation [10]. Reasons for this are that some degree of nocturia may be considered part of the normal aging process and/or many may be embarrassed or hesitant to discuss symptoms [13, 14].

In the current study, the median nocturia episodes were four; the average age of patients was 71 although the range of patients was quite large and 60% were female. We found that half of the patients had been on medical therapy for the lower urinary tract prior to seeking treatment with a certified specialist. Increasing age and BMI were associated with a higher baseline nocturia number. Almost 2/3 of patients had underlying conditions that may have contributed to nocturia, most commonly a cardiac history.

At follow-up visits, subjective patient reported improvement was not correlated with age, BMI, prior treatment, or any particular therapy at any visit. However, improvement was associated with completion of the third visit. This was a modest improvement considering the time and likely multiple treatments attempted at improving this symptom. The improvement of one less nocturia episode per patient from the first to third visit is in line with improvements seen with anticholinergics and alpha blockers when studied in OAB or BPH studies where patients may have had concurrent nocturia. For example, efficacy in a study of more than 1000 men with BPH, terazosin, finasteride and the combination of both was only nominally more effective at reducing nocturia episodes compared to placebo [15]. Nocturia decreased from a baseline mean of 2.5 voids per night to 1.8, 2.1, 2.0 and 2.1 episodes per night in the terazosin, finasteride, combination and placebo groups, respectively. Similarly, antimuscarinic agents aim to target those with a decreased nighttime bladder capacity, but have also shown minimal effect on nocturnal voids. A study comparing trospium to placebo found reduced nocturia episodes, an average of 0.57 per night compared to 0.29 with placebo [8]. While many therapies have been found to be statistically significant versus placebo, their clinical significance remains questionable.

Over 50% of patients in the current study did not return for a third visit. With myriad treatment options that are marginally effective, these may be used in a "trial and error" fashion, which may lead to frustration and thus failure to follow-up. Likely there were many failures in patients who did not follow-up or perhaps patients decide behavioral treatments are not worth the effort. The motivated patient that returns for follow-ups appears to fare better as therapies may be targeted.

Bladder diaries remain the best tool to narrow the pathophysiological mechanisms for nocturia into nocturnal polyuria, global polyuria, diminished bladder capacity or mixed nocturia (NP and low bladder capacity). In this series, BD was utilized in only 50% of patients. Similar rates were found in both large American and European cohorts where patients evaluated by a urologist completed a diary only 45% of the time [10]. In the current study, utilization of a BD was highly correlated to the specific provider. This indicates distinct practice patterns on a common diagnosis. However, we could not capture clinician assessment of patients' willingness or ability to complete a BD, which likely contributed to these low rates. Patient compliance with paper BD was 63%. 76% of patients met the criteria for NP, and 21% with a diagnosis of OAB/reduced capacity. This is consistent with the Krimpen study which followed 1688 men for up to 6 years and found a prevalence of NP in 77.8% [16]. We found that higher NPI score was associated with greater improvement in nocturia over three visits; these patients may be more responsive to pharmacologic and non-pharmacologic treatment or potentially less likely to have a primary sleep disorder. Nonetheless, less than 50% of patients reported improvement, regardless if they completed a BD, suggesting that while therapy may be targeted, the effect is modest. If most patients complaining of nocturia have NP and diary use did not improve outcomes in the current study, the clinical use may be questioned by some providers. However, if a thorough medical, medication, voiding and fluid consumption history is still taken, this may be satisfactory to focus therapy. Furthermore, focused therapy is limited especially with respect to medical treatment for NP. For those who did complete a BD, our follow-up of three visits may not have been sufficient time for treatment to take effect or allow for drug/dose modifications. With or without an BD, patient improvement and retention rates were low. We believe that BD remains the gold standard diagnostic tool for NP and expect increased utilization as treatments expand.

The current study shows that treatment for nocturia is often ineffective and suboptimal. Pointed medication towards overproduction of urine has the most potential for filling this gap with new therapies on the horizon. Desmopressin, a synthetic analog of arginine vasopressin, benefits patients with central diabetes insipidus, primary nocturnal enuresis and nocturia [7]. Multiple randomized placebo controlled trials have shown that it is a safe and efficacious drug [17, 18]. One trial showed a reduction of 1.43 mean nocturnal voids per night compared to placebo with a reduction of

0.86 voids [17]. We found that the desmopressin formulation available at the time of the study was prescribed in only 5% of all patients. This was an off-label use and may have contributed to patient and provider reluctance to use such medication. A large database of US and European patients consisting of 8659 patients seeking treatment for LUTS showed that 3–18% were prescribed antidiuretics, while antimuscarinics were most commonly utilized in women and alpha blockers in men [10]. This suggests an underutilization of this targeted therapy. However, we found no significance with patient reported improvement or change in nocturia number with any particular therapy. This suggests the fact that currently employed medical approaches for the treatment of nocturia have poor efficacy and are not targeted for overproduction of urine. The introduction of newly approved Noctiva™ (desmopressin acetate nasal spray with a permeation enhancer) has the potential to affect clinical practice. The newly engineered medication has a highly predicable pharmokenetic profile and, thus, low rates of hyponatremia with the same effect as available desmopressin tablets [19]. Improved attentiveness to NP with new therapies could hasten pharmacologic benefit.

This real clinical assessment of diagnosis, treatment and outcomes can help the physician understand the pathway of nocturia patients that often leads to modest improvement or failure to follow-up. A better understanding of this diverse population is needed to help target therapy. More than half of our population had comorbidities that were potential factors underlying nocturia; however, we were unable to capture the extent that these risk factors played in counseling and focused therapy. The failure to achieve greater success improving nocturia leaves us with questions. Were patients that received more counseling more likely to follow-up and potentially be "responders"? Do we need to stratify patients beyond the ICS definition of nocturia? Are there subpopulations that can be empirically treated with newer therapies based on a history and limited examination alone? Should desmopressin be restricted to those only with diary-confirmed nocturnal polyuria? Guidelines and consensus statements are useful tools for clinicians and may need to be reconsidered as we find out more about therapies now aimed at reducing urine production. To make these updates most meaningful, hopefully we will have more data on objective symptom improvement but also information on the impact on quality of life.

Limitations of this study include the retrospective nature and high risk for selection bias. We do not know the rate of success or failure in the large number of patients who did not return for follow-up. Furthermore, there was no standardized patient quality of life measure, nocturia score, LUTS assessment or sleep quality index outcome used. As with many studies looking at lower urinary tract symptoms, we used a global improvement assessment in addition to patient-reported nocturia episodes. It is hard to know how much the continued conservative therapy reinforcement helps with the improvement over time or medication adjustment. This was not necessarily standardized across patients and we have no way of assessing the adherence to these therapies. The study demonstrates that our prescribed use of treatments directed towards nocturnal polyuria is modest at best, or behavioral therapies that are directed toward NP are not complied with and follow-up is poor.

Conclusion

Nocturia is a highly prevalent symptom associated with many different disease processes and is associated with significant sequelae and morbidity. Success is relative to each patient and depends on the baseline condition. Currently employed measures tend to be nonspecific as half of patients do not complete a BD and responses to therapy are suboptimal. Further work is needed to increase patient satisfaction and target treatment of this prevalent condition.

Acknowledgements None.

Author contributions SD protocol/project development, data collection, data analysis, manuscript writing/editing. BP manuscript writing/editing. AR data collection, data analysis. NR data collection. VN data collection, manuscript writing/editing, data analysis. BB protocol/project development, manuscript writing/editing

Funding There was no source of funding from any company.

Compliance with ethical standards

Conflict of interest Siri Drangsholt: None; Maria Juliana Arcila Ruiz: None; Benjamin Brucker: Avadel, Serenity, Allergan, Medtronic, Watkins-Conti, Ipsen; Avadel- Consultant and Speaker; Serenity—Consultant; Allergan—Speaker, Consultant, Investigator; Metronic-Investigator; Watkins-Conti- advisor; Ipsen—Investigator; Victor Nitti: Owns stock in Serenity; Benoit Peyronnet: Astellas, Medtronic, Allergan, Boston Scientific, Ipsen; Astellas—Consultant; Allergan—Consultant; Metronic—Consultant; Boston Scientific—Consultant; Ipsen—Investigator; Nirit Rosenblum: None.

Ethical approval This study was approved by the New York University Institutional Review Board as it involved research on human subjects.

Informed consent This study was retrospective using de-identified data and thus informed consent was not needed.

References

1. Cornu J-N et al (2012) A contemporary assessment of nocturia: definition, epidemiology, pathophysiology, and management–a systematic review and meta-analysis. Eur Urol 62:877–890

2. DuBeau CE, Yalla SV, Resnick NM (1995) Implications of the most bothersome prostatism symptom for clinical care and outcomes research. J Am Geriatr Soc 43:985–992
3. Tikkinen KAO et al (2010) Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 57:488–496
4. Nimeh T, Alvarez P, Mufarreh N, Lerner LB (2015) Nocturia: current evaluation and treatment for urology. Curr Urol Rep 16:66
5. van Kerrebroeck P et al (2002) The standardisation of terminology in nocturia: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 21:179–183
6. Bosch JLHR, Weiss JP (2013) The prevalence and causes of nocturia. J Urol 189:S86–S92
7. Aizen J, Lee CL, Olugbade K, Weiss JP (2015) AUA update series 2015, evaluation and management of nocturia. Lesson 38:34. https://auau.auanet.org/node/4884. Accessed 9 Dec 2016
8. Rudy D, Cline K, Harris R, Goldberg K, Dmochowski R (2006) Multicenter phase III trial studying trospium chloride in patients with overactive bladder. Urology 67:275–280
9. Eisenhardt A, Schneider T, Cruz F, Oelke M (2014) Consistent and significant improvement of nighttime voiding frequency (nocturia) with silodosin in men with LUTS suggestive of BPH: pooled analysis of three randomized, placebo-controlled, double-blind phase III studies. World J Urol 32:1119–1125
10. Oelke M, Anderson P, Wood R, Holm-Larsen T (2016) Nocturia is often inadequately assessed, diagnosed and treated by physicians: results of an observational, real-life practice database containing 8659 European and US-American patients. Int J Clin Pract 70:940–949
11. Jimenez-Cidre MA et al (2015) The 3-day bladder diary is a feasible, reliable and valid tool to evaluate the lower urinary tract symptoms in women. Neurourol Urodyn 34:128–132
12. Jayadevappa R, Newman DK, Chhatre S, Wein AJ (2015) Medication adherence in the management of nocturia: challenges and solutions. Patient Prefer Adherence 9:77–85
13. Chen F-Y et al (2007) Perception of nocturia and medical consulting behavior among community-dwelling women. Int Urogynecol J Pelvic Floor Dysfunct 18:431–436
14. Wennberg A-L et al (2009) Lower urinary tract symptoms: lack of change in prevalence and help-seeking behaviour in two population-based surveys of women in 1991 and 2007. BJU Int 104:954–959
15. Johnson TM et al (2003) Changes in nocturia from medical treatment of benign prostatic hyperplasia: secondary analysis of the Department of Veterans Affairs Cooperative Study Trial. J Urol 170:145–148
16. van Doorn B, Kok ET, Blanker MH, Westers P, Bosch JLHR (2014) Determinants of nocturia: the Krimpen study. J Urol 191:1034–1039
17. van Kerrebroeck P et al (2007) Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 52:221–229
18. Weiss JP, Zinner NR, Klein BM, Nørgaard JP (2012) Desmopressin orally disintegrating tablet effectively reduces nocturia: results of a randomized, double-blind, placebo-controlled trial. Neurourol Urodyn 31:441–447
19. Noctiva [package insert] (2017). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/201656lbl.pdf. Accessed 1 May 2018