

## Review Article

### NOCTURIA

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#### ABSTRACT

**Purpose:** We review the current state of knowledge of nocturia and present algorithms for diagnosis, classification and treatment.

**Materials and Methods:** We reviewed the recent literature on nocturia, and state-of-the-art methods of diagnosis, classification and treatment.

**Results:** Nocturia, which is among the most bothersome of all urological symptoms, has heretofore been poorly classified and understood. Multiple factors may result in nocturia, including pathological conditions, such as cardiovascular disease, diabetes mellitus, lower urinary tract obstruction, anxiety or primary sleep disorders, and behavioral and environmental factors. Nocturia may be attributed to nocturnal polyuria (nocturnal urine overproduction) and/or diminished nocturnal bladder capacity. Distinction between these conditions is made by a simple arithmetic analysis of a 24-hour voiding diary.

**Conclusions:** Nocturia has been poorly studied, and its etiology and pathogenesis have been classified only recently. We present a scheme for diagnosis and care of patients suffering from loss of sleep due to nocturnal voiding.

**KEY WORDS:** urination disorders, enuresis, aged, therapeutics

A common reason for interrupted sleep in the general adult population is nocturia, that is waking during the night to urinate.<sup>1,2</sup> Many individuals with nocturia, particularly elderly men, have other lower urinary tract symptoms, such as urinary frequency, weak stream, urgency, incontinence and so forth. In women these symptoms are often considered to result from aging, childbirth or just “being a woman.”<sup>3,4</sup> In men they are most often attributed lower urinary tract symptoms suggestive of benign prostatic obstruction. For patients with nocturia the process of symptom normalization often involves severe fluid restriction during the evening at the cost of increased thirst to limit the number of nighttime voiding episodes.<sup>5–7</sup> As a result of this acceptance of symptoms, patients may not report the condition to medical professionals until it becomes unbearable for them or their caregivers, or when resultant daytime sleepiness affects work or quality of life.<sup>3</sup> Treatment of nocturia typically involves attempts to resolve detrusor instability or bladder outlet obstruction. However, while either or both of these etiologies may exist in the individual complaining of nocturia, treatment may fail due to an often overlooked component of nocturnal polyuria.

Nocturia refers to the simple notion of urinating during the night and a more complex idea involving some sort of excess. It is unclear if the excess refers to the volume of urine being produced or voided, or number of occasions when urine is passed. What constitutes an excessive frequency or volume for nocturnal urination has not been well defined for any age group to our knowledge and especially not for the elderly.<sup>8,9</sup>

Nocturia is a common reason for urological consultation.<sup>10</sup> The majority of patients are elderly and more likely to be exposed to serious health risks since nocturia causes fatigue due to sleep deprivation, which increases the chance of traumatic injury through falling.<sup>11</sup> In a study of nighttime falls of the elderly those with nocturia were at a significantly greater

risk of falling, increasing from 10% to 21% with 2 or more voids per night.<sup>12</sup> Falling often leads to fractures, particularly hip fractures, which are a serious consequence of an already bothersome condition.

Pathological conditions causing nocturia include cardiovascular disease, diabetes mellitus and insipidus, lower urinary tract obstruction and awakening to void for other reasons, such as anxiety or primary sleep disorders.<sup>2,11,13,14</sup> Behavioral and environmental factors contributing to nocturia include consumption of diuretic medication, caffeine, alcohol or excessive fluid shortly before retiring for the night.<sup>11</sup> Prostatic disease, and neurogenic and unstable bladders have been reported to lead to frequent nocturnal rising.<sup>11,13</sup> In addition, nocturia may result from stroke, congestive heart failure, peripheral edema (for example due to venous insufficiency or nephrosis) and myeloneuropathy secondary to vertebral disk disease or spondylosis.<sup>15</sup>

*Effects of sleep deprivation.* Sleep is important for physical and mental well-being. It is generally thought that adults need about 7 to 8 hours sleep per night and that adequate sleep has a restorative effect. The quality of sleep deteriorates with increasing age and older adults have shallower and more fragmented sleep patterns, possibly as a result of the reduction in growth hormone secretion with age.<sup>16</sup> Few physiological changes are seen with sleep loss and mainly are noted with total sleep as opposed to partial sleep deprivation, including changes in temperature regulation, mood status (temporary euphoria in depressed subjects) and central nervous system function (paranoia, delusions).<sup>17</sup> However, insufficient or disrupted sleep has commonly been linked with physical and mental disorders, particularly depression and mood alterations,<sup>18,19</sup> as well as excessive daytime sleepiness leading to poor motivation and job performance.<sup>17,19,20</sup> A connection between chronic somatic disease and sleep complaints has previously been made.<sup>21,22</sup> A study of patients 50

to 65 years old concluded that apnea and daytime sleepiness were indicators of disease and lower psychosocial function.<sup>23</sup> A study of premenopausal and postmenopausal women indicated that daytime sleepiness was 3 times higher in those who woke 3 or more times a night to urinate compared to those who did not awaken.<sup>7</sup> In addition, these women had a worse general state of health and were sick more frequently. The number of sick days taken was related to the number of nighttime voids, with up to 75 sick days a year for 3 or more voiding episodes (fig. 1). A questionnaire completed by a large Dutch cohort older than 50 years revealed that worrying and nocturia were the 2 factors most responsible for disturbed sleep.<sup>1</sup> The number of nighttime awakenings increased with age, most noticeably in men, although women reported poorer overall quality of sleep. In cases of persistently reduced sleep quality daytime napping may be related to somatic disease.<sup>7</sup>

**Bothersomeness.** The incidence and bothersomeness of nocturia have been reported in studies of men with nocturia. Nocturia was reported by 73% of patients without prostatic obstruction and was the fourth most common symptom after decreased stream, dribbling and urgency in the study of Du Beau et al.<sup>24</sup> They concluded that prostatic surgery in these patients would not reduce the bothersomeness of nocturia since it was often not due solely to obstruction. Another study demonstrated that nocturia at least twice nightly was the second most bothersome symptom associated with benign prostatic obstruction, although it was not reported as frequently as other symptoms, such as terminal dribbling, hesitancy or urgency.<sup>25</sup> A study of 2,075 United Kingdom women older than 19 years also showed that nocturia twice nightly or more was "at least a bit of a problem" for 62.6%.<sup>26</sup> No relationship was noted between age and bother, implying that nocturia is bothersome for all age groups.

Regardless of cause, more than 72% of the elderly arose at least once a night with the urge to void and 24% routinely arose 3 or more times.<sup>11,27</sup> Of women 40 to 60 years old 55% had nocturia, including 75% who were mildly, 21% moderately and 4% greatly bothered. In addition, 95% of women with nocturia arose once or twice nightly. Of these women 22% considered it a problem and 2% considered it a serious problem. The remaining 5% of women arose more than twice to void. Of these women 83% considered nocturia a problem and 37% considered it a serious problem.<sup>28</sup> A recent survey of adults with nocturia revealed that 71% to 82% of responders had nocturia, including 22% to 51% who

found it bothersome. More than 50% of patients from the United States and Germany were likely to consult a physician for symptoms in contrast to only 22% and 24% of those from Sweden and France, respectively.<sup>29</sup>

**Epidemiology.** The high prevalence of urinary symptoms in older patients has resulted in a nearly exclusive evaluation of these problems in the elderly. Of men 60 to 69 years old 22% and of those 70 to 85 years old 29% reported a voiding frequency of twice nightly or more, which was a statistically significant difference. Patients with several symptoms tended to be diagnosed with prostatism.<sup>30</sup> More recently nocturia, sleep and well-being in women 40 to 64 years old were studied. These women often begin to experience urinary problems due to menopause. Nocturia was reported by 67% of the subjects, with 14.7% voiding 2 or more times per night. The incidence of nocturia and the total number of voiding episodes increased with age, and increased well-being was associated with fewer voids and better quality of sleep.<sup>7</sup> In contrast, the frequency of nocturia in women 20 to 80 years old was highlighted in a quality of life analysis using the International Prostatic Symptom Score in which age was not found to influence the number of voids. It was concluded that 1 to 2 nocturnal voiding episodes per night were not pathological since this was a general baseline level of nocturia experienced by the majority of women.<sup>31</sup> Nocturia twice nightly or more increased significantly with age in women older than 19 years in a mail questionnaire study.<sup>32</sup> The authors also concluded that, with regard to nocturnal voiding, a redefinition of normal is necessary. A study of male and female volunteers older than 30 years revealed that the prevalence of nocturia increased with age in men and women.<sup>33</sup> A United States survey of 400 healthy men 60 years old or older revealed that 65.2% voided during the night and 25% voided more than 2 times nightly, while of 479 healthy women surveyed 62.8% reported nocturnal voiding, including 24% who voided 2 or more times nightly.<sup>4</sup> Because of this perceived correlation with increasing age nocturia is often viewed as a natural part of aging, although it may occur at a young age, which contributes to a lack of help seeking behavior.

#### MECHANISMS OF NOCTURIA

Although in many cases nocturia may be caused by bladder dysfunction (for example inflammation or prostatic obstruction) or sleep apnea,<sup>34</sup> simple overproduction of urine during the night is another common etiology.<sup>6</sup> There are 3 broad categories of pathophysiology which account for nocturia, which we refer to as nocturnal polyuria, low nocturnal bladder capacity and mixed nocturia (a combination of nocturnal polyuria and nocturnal bladder capacity). These categories are generated through interpretation of a single 24-hour voiding diary in which each voided volume is tabulated with corresponding time as to whether voiding was within hours awake or asleep. We carefully counsel each patient (or, if elderly or infirm, the primary caregiver) about the procedure for diary procurement and review the likelihood that the diary is representative of the typical situation. Thus, we avoid having to obtain multiple diaries which we find diminishes compliance. An algorithm for analysis of nocturia is presented in figure 2. Polyuria, defined as 24-hour urine output greater than 2,500 ml.,<sup>35</sup> may cause nocturia through generally increased urine production when nocturnal urine output exceeds functional bladder capacity as it does with nocturnal polyuria. However, polyuria and nocturnal polyuria are not mutually inclusive.

**Nocturnal polyuria.** The nocturnal polyuria syndrome was defined by Asplund as increased urine output during the night.<sup>6</sup> However, in contrast to diabetes insipidus (when intake and output are increased), 24-hour urine production

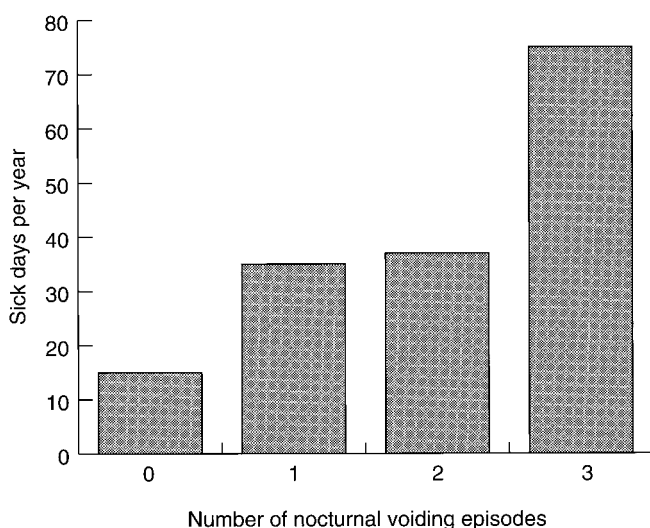


FIG. 1. Number of sick days taken off work by women 40 to 64 years old according to number of nighttime voids. Reprinted with permission.<sup>7</sup>

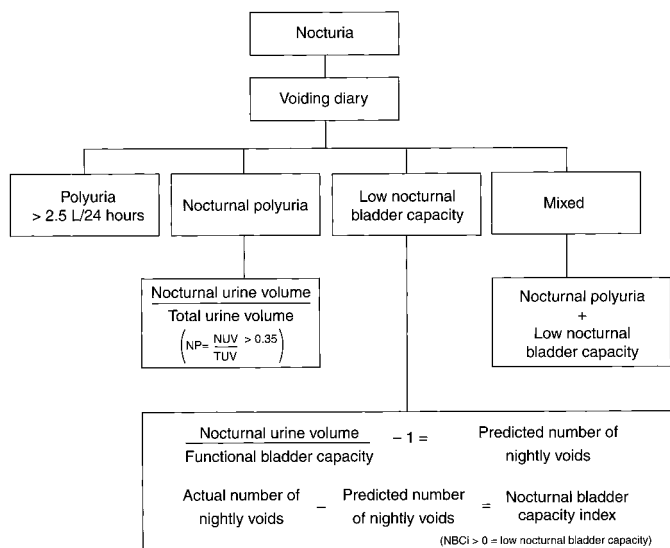


FIG. 2. Algorithm for voiding diary analysis of causes of nocturia. *NUV*, nocturnal urine volume. *TUV*, total urine volume. *NP*, nocturnal polyuria.

remains normal, indicating a variation in normal diurnal production of urine. This increased nocturnal diuresis results in nocturnal urine volume in excess of bladder capacity, creating the need for nighttime voiding in the form of nocturnal enuresis or nocturia.<sup>36</sup> Several definitions of nocturnal polyuria have been used, such as nocturnal urine volume in excess of 6.4 ml./kg.<sup>14</sup> or exceeding a third of the total daily urine output<sup>13</sup> and nocturnal diuresis 0.9 ml. or greater per minute<sup>37,38</sup> but none has achieved widespread acceptance. Our preferred definition is when nocturnal urine volume is more than 35% of the total 24-hour urine production and we define the nocturnal polyuria index as nocturnal urine volume (*NUV*) per 24-hour urine greater than 0.35.<sup>35,39</sup> Another precise definition characterizes nocturnal polyuria according to the exact number of hours asleep and the fraction of urine output that would be expected during this time:

$$NUV > \left( \frac{\text{Number of hours sleep}}{24} \right) \times 24 \text{ hour urine volume}$$

When assessing a voiding diary, the first morning void is included in the nocturnal urine volume since this void was excreted by the kidneys during sleep. However, the first morning void is considered a normal diurnal voiding episode not to be included with the tally of actual number of nightly voids. Still another approach to nocturnal polyuria is to grade nocturnal urine overproduction as a function of bladder capacity with the recently developed nocturia index, which is defined as nocturnal urine volume divided by functional bladder capacity.<sup>35</sup> If nocturia index is greater than 1, nocturia occurs due to nocturnal urine output in excess of bladder maximal storage capacity, which may be due to increased nocturnal urine production and/or reduced bladder capacity.<sup>40</sup> The causes of nocturnal polyuria are listed in Appendix 1.

Increased production of urine at night with nocturnal polyuria is offset by decreased daytime production, such that the 24-hour urine volume remains normal.<sup>6</sup> The reason for this diurnal change is thought to be a disruption of the diurnal variation in secretion of arginine vasopressin. Arginine vasopressin, which is normally secreted in a diurnal pattern, is partly responsible for regulation of urine production.<sup>41</sup> Since arginine vasopressin increases resorption of water from the renal tubule, higher concentrations at night result in the production of lower volumes of concentrated urine.

A change in the diurnal pattern of arginine vasopressin

secretion has been noted in the elderly.<sup>13,14,42</sup> However, there is controversy surrounding its role in regard to onset of nocturia in elderly subjects since other contributory factors, such as benign prostatic hyperplasia (BPH),<sup>43</sup> bladder dysfunction and reduced thirst perception, may coexist.<sup>44,45</sup> Plasma arginine vasopressin is often undetectable during the night in elderly subjects with nocturia, thus implying a cause and effect relationship between its secretion and nocturnal polyuria.<sup>13,46</sup>

Nocturia in a large proportion of elderly men with lower urinary tract symptoms is caused by nocturnal polyuria and natriuresis.<sup>14</sup> Interestingly, a positive correlation has been observed between nocturnal urine volume and daytime mean arterial blood pressure. While significant negative correlation has been found between nocturnal urine volume and plasma angiotensin II, nocturnal polyuria is associated with decreased plasma arginine vasopressin.<sup>14</sup> A possible explanation for nocturnal polyuria and natriuresis in these patients is that pressure induced lesions in the renal medulla and distal tubular system may be caused by long lasting urinary tract obstruction, which may interfere with normal circadian renal handling of sodium by decreasing diurnal sodium excretion.<sup>14</sup>

Respiratory diseases associated with increased airway resistance, such as obstructive sleep apnea, are associated with increased renal sodium and water excretion mediated by plasma atrial natriuretic peptide.<sup>14,47</sup> The prevalence of obstructive sleep apnea is about 2% in women and 4% in men.<sup>48</sup> The mechanism for elevated atrial natriuretic peptide release associated with obstructive sleep apnea has been demonstrated as due to increased right atrial transmural pressure resulting from hypoxia induced pulmonary vasoconstriction.<sup>47</sup> Hence, a population of patients with nocturia may result from obstructive sleep apnea and secondary nocturnal polyuria.<sup>49</sup> Therefore, polysomnographic sleep studies are recommended in patients with nocturia suspected of obstructive sleep apnea. Patient selection is based on increased risk, and those with morbid obesity, acromegaly, asthma, hypertension, adult onset diabetes mellitus and craniofacial abnormalities may undergo sleep studies due to the 30% to 40% chances of having obstructive sleep apnea.<sup>48</sup>

Nocturnal polyuria may be occasioned by third spacing of fluid in the lower extremities caused by right congestive heart failure and lower extremity venous stasis disease. Detailed history and physical examination as well as adjunctive testing, such as cardiac echography and nuclear testing, should be used in patients with nocturnal polyuria who are at risk for cardiac disease. Similarly, patients with primary thirst disorders (for example, those taking lithium) may present with global polyuria and secondary nocturnal polyuria.<sup>50</sup> Diagnosis may be made by careful diary evaluation of intake and urinary output in addition to use of the renal concentrating capacity test. In adults 40  $\mu$ g. desmopressin are administered intranasally. The bladder is emptied and a urine sample for osmolality is obtained 3 to 5 hours later. Water intake is restricted for the first 12 hours after drug administration. The reference level for normal urine osmolality after desmopressin administration is 1,000 mOsm/kg. for most patients. Post-desmopressin administration urine osmolality less than 550 mOsm/kg. suggests central or renal diabetes insipidus whereas less than 800 is consistent with psychogenic polydipsia. However, after several days of desmopressin administration patients with central diabetes insipidus have normal concentrating capacity.<sup>51,52</sup>

*Diminished nocturnal bladder capacity.* Problems with low nocturnal bladder capacity exist when nocturnal voiding occurs at bladder volumes less than functional bladder capacity.<sup>53</sup> Nocturia index is nocturnal urine volume /functional bladder capacity, with the first morning void included in the nocturnal urine volume. Nocturia index minus 1 equals the predicted number of nightly voids. The nocturnal bladder capacity index

is defined as the difference between the predicted number of nightly voids and the actual nightly voids (ANV). The significance of this difference is that the greater the nocturnal bladder capacity index, the more nocturia may be attributed to diminished nocturnal bladder capacity and sensory urge disorders. For example, if nocturnal urine volume is 1,000 ml. and functional bladder capacity is 500 ml., nocturia index is  $1,000/500 = 2$ . This patient would have a predicted number of nightly voids equal to 1 (nocturia index - 1 = 1) and would be expected to void once per night, that is the first 500 ml. during sleep hours and the second 500 ml. with the first morning void. For example, if the patient actually arose 7 times to void the same 1,000 ml., he or she would have a nocturnal bladder capacity index of 6 (7 actual - 1 predicted number of nightly voids). This patient, for whatever reason, has significantly diminished bladder capacity during sleep hours. Thus, a high nocturnal bladder capacity index indicates diminished nocturnal bladder capacity or more severe sensory urgency. The causes of decreased nocturnal bladder capacity are listed in Appendix 2.

Many patients with nocturia have a combination of nocturnal polyuria and low nocturnal bladder capacity, which we refer to as a mixed etiology of nocturia. Treatment of these patients should be directed at both disorders.

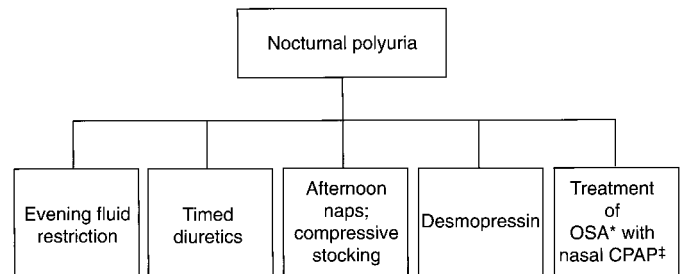
#### DIAGNOSIS

Patients are likely to present to the clinician with direct or indirect symptoms, such as insomnia, daytime tiredness or related somatic disease. Evaluation of nocturia begins with a focused history and physical examination considering various aspects, such as sleep, urinary problems, fluid intake, cardiac problems, medication, prior lower urological tract surgery, other conditions and co-morbidities, which might account for excessive nocturnal urine output, detrusor overactivity or sensory urgency. Of paramount importance is the voiding diary, without which the differential diagnosis of nocturia cannot be made. On the basis of the voiding diary, the patient is categorized as having polyuria, nocturnal polyuria, low nocturnal bladder capacity or a mixed disorder. The evaluation for various causes of nocturnal polyuria includes a history, and physical and laboratory examinations designed to evaluate the patient for symptoms and signs of congestive heart failure, diabetes, renal insufficiency, venous insufficiency and obstructive sleep apnea (Appendix 1). When diabetes insipidus is suspected, water deprivation, solute loading tests or the renal concentrating capacity test may be used.<sup>54</sup> Evaluation for etiology of diminished nocturnal bladder capacity (yielding an increased nocturnal bladder capacity index) is more related to endoscopic and urodynamic techniques for diagnosing vesical inflammatory, neoplastic or functional disorders (Appendix 2). Blaivas et al recently reported that there is no correlation between urodynamic parameters of urethral obstruction and detrusor contractility/instability, and nocturia severity or etiology indexes.<sup>55</sup> This finding suggests that nocturnal urodynamic and sleep studies may yield more relevant information required in classification and treatment of nocturia due to diminished nocturnal bladder capacity.

#### THERAPEUTIC STRATEGIES

Current treatment options for nocturia depend on the diagnosis. Nocturia due to nocturnal polyuria is rarely diagnosed as a primary complaint and, therefore, few studies consider its therapy. Indeed, most currently available therapies treat only the symptoms and not the cause of nocturia. Treatment of nocturia is directed by algorithms.

*Nocturnal polyuria* (fig. 3). Remediable medical causes of nocturnal polyuria should be identified and treated (Appendix 1) but in some cases nocturia persists and in most clearly identifiable remediable conditions are not evident. Empirical treatment options include evening fluid restriction (a form of



\* Obstructive sleep apnea

‡ Continuous positive airway pressure

FIG. 3. Treatment of nocturnal polyuria

behavior modification), timed diuretics,<sup>56,57</sup> afternoon naps and/or elevation of the legs, application of compressive stockings when appropriate and antidiuretic hormone administration.<sup>5,6,13,27,58</sup> The latter should be avoided or used judiciously at best in patients with congestive heart failure.

In the elderly simple fluid restriction is rarely effective to reduce nocturnal polyuria which is due to the mobilization of gravitational induced third space of interstitial fluid residing in the lower extremities upon achieving a recumbent position. Compressive devices may prevent this fluid accumulation and help diminish nocturnal urinary output. In addition, late afternoon naps with elevation of the legs simulate sleep hours during the day and may diminish the burden of fluid excretion otherwise inevitable during normal sleep time. If edema is present in the legs or presacral area, diuretics may be helpful to diminish this third spacing. All diuretics act within 2 hours of administration and, therefore, may be given in mid to late afternoon or early evening as they are least needed just after arising and may exacerbate nocturnal polyuria if given later in the evening. Bumetanide reduced by 4 the number of weekly nighttime voids in patients without obstructive symptoms.<sup>54</sup> In addition, furosemide has been effective in reducing nocturia and nocturnal polyuria.<sup>56</sup> Doses of the diuretic taken 6 hours before bedtime reduced the number of nighttime voids by 0.5 and lowered the percentage nighttime voided volume by 18%. Recent evidence has been presented for treatment of nocturnal polyuria with imipramine.<sup>59</sup> The mechanism for such antidiuretic effect is thought to result from imipramine mediated  $\alpha$ -adrenergic stimulation in the proximal nephron with increased urea and water reabsorption in the distal nephron.

Patients with nocturia caused by nocturnal polyuria mediated by obstructive sleep apnea and secondarily increased plasma atrial natriuretic peptide may expect to benefit from nocturnal treatment with nasal continuous positive airway pressure.<sup>60,61</sup> While such treatment of obstructive sleep apnea would seem to be effective to correct nocturia, to our knowledge formal studies are lacking. However, a recent report associates treatment of obstructive sleep apnea using nasal continuous positive airway pressure with resolution of nocturnal enuresis.<sup>62</sup>

Exogenous administration of antidiuretic treatment is effective to prevent nocturnal polyuria. Desmopressin (1-deamino-8-day-arginine-vasopressin) is an arginine vasopressin analogue that has been proved effective and well tolerated to treat neurogenic diabetes insipidus<sup>63-71</sup> and enuresis in children<sup>72-86</sup> and adults.<sup>86,87</sup> Desmopressin also reduced or eliminated nocturnal voiding in patients with autonomic dysfunction<sup>88,89</sup> and Parkinson's disease.<sup>90</sup> Patients with nocturia due to multiple sclerosis have been successfully treated with desmopressin, with a decrease in the number of voids per night and corresponding increase in nights free from voiding and hours of uninterrupted sleep.<sup>91-94</sup> In addition, patients previously diagnosed with

BPH had fewer voids when treated with desmopressin, particularly those with high nocturnal urine output.<sup>95</sup> Desmopressin therapy has also been successful for treating women with nocturia after antispasmodic medication failed.<sup>96</sup> The success of desmopressin for these indications and an increased awareness of the use of voiding diaries for the diagnosis of voiding dysfunction in general have led to its use to treat nocturia specifically due to nocturnal polyuria.<sup>5,6,96</sup> Initial<sup>35,97</sup> and more recent<sup>37,38,98</sup> studies noted a decrease in nocturnal urine volume in adults treated with desmopressin, which was more marked in those with greater degrees of pretreatment nocturnal diuresis.

Our protocol begins with 10  $\mu\text{g}$ . desmopressin intranasally or 0.1 mg. orally increased by increments of 10  $\mu\text{g}$ . or 0.1 mg., respectively, every third night until the desired effect is reached, to a maximum dose of 40  $\mu\text{g}$ . or 0.4 mg., respectively, every bedtime (fig. 4). The patient is seen again in the late afternoon after dose 1 because electrolyte abnormalities or fluid overload is most likely to commence then. Even if the patient is asymptomatic, serum electrolytes should be measured the day following dose 1 and the patient should be questioned about headache, nausea, vomiting, lightheadedness and so forth. If any of these symptoms occur, the medication should be discontinued until laboratory results are known. It seems prudent to recheck electrolytes 1 week into therapy with desmopressin. The patient or caregiver should be taught to monitor the legs and presacral area for edema, and daily weight for early identification of excess fluid retention induced by desmopressin in susceptible patients. Significant weight increases, new onset or worsening of edema or symptoms of hyponatremia, such as headache or visual disturbance, should be reported immediately to the physician and the medication should be discontinued. The aforementioned protocol may be prescribed to appropriately selected patients with nocturia due to nocturnal urine overproduction who are 21 years old or older.

In our opinion claims of lack of side effects from antidiuretic treatment apply to pediatric patients with enuresis and cannot be expected in the elderly, especially those with a history of congestive heart failure. It is important to remind patients receiving desmopressin that they should sharply curtail evening water intake to minimize fluid retention. Despite these caveats, a recent study indicates the general lack of side effects resulting from treatment of elderly men and women (mean age 72 and 73 years, respectively) with nocturnal polyuria using 40  $\mu\text{g}$ . desmopressin during a 2-month interval.<sup>99</sup>

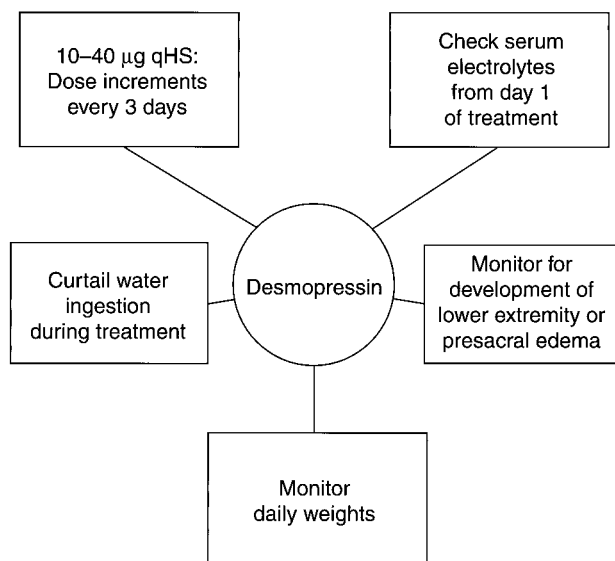


FIG. 4. Program for treatment of nocturnal polyuria using desmopressin. *qHS*, every bedtime.

Mannucci was the first to demonstrate the therapeutic value of desmopressin to treat and prevent bleeding complications in patients with mild forms of hemophilia A and von Willebrand's disease.<sup>100</sup> However, the doses of desmopressin used to treat coagulation disorders are about 10 times higher than those recommended for antidiuretic therapy. Thus, it is unlikely that dosage levels of desmopressin used to treat nocturnal polyuria would be associated with thrombotic complications. The efficacy of any combination of the aforementioned treatment methods for nocturnal polyuria may be easily determined using repeat voiding diaries.

**Polyuria.** Polyuria, defined as 24-hour urine output in excess of 2,500 cc, is related to increased intake so that polyuria and polydipsia (at least in the steady state) are closely related. Thus, polyuria results in day and night urinary frequency due to global urine overproduction in excess of bladder capacity. Causes of polyuria include diabetes mellitus and insipidus (in turn due to deficient production of vasopressin by the pituitary or primary nephrogenic water loss), lithium induced polydipsia/polyuria<sup>50,52</sup> and primary thirst disorders.<sup>101</sup> While polyuria causes increased nocturnal urine volume, like nocturnal polyuria, treatment is directed at reduction in water intake and its resultant output through specific measures, such as insulin replacement, voluntary restriction of water intake or supplementary administration of vasopressin analogues when appropriate.

**Diminished nocturnal bladder capacity.** We have noted a significant association of severe nocturia with nocturnal bladder capacity index greater than 2 (unpublished data). Thus, we recommend evaluation for and treatment of causes of diminished nocturnal bladder capacity in patients with nocturia and an index greater than 2. A patient with significantly low nocturnal bladder capacity may be expected to have bladder outlet obstruction, detrusor instability, sensory urgency or primary bladder disorders, such as infection, inflammation or malignancy. Specific treatment of the underlying urological condition would then be expected to have a mitigating effect on decreased nocturnal bladder capacity as a component of nocturia. For many elderly men prostatism is considered to be the primary cause of nocturia, often despite insufficient investigation. Therapy for these patients involves surgery, which reduces problems associated with obstruction, such as poor stream and incomplete voiding, but often does little to reduce the more irritative symptoms, such as nocturia and frequency. Thus, whereas Bruskewitz et al reported improved voiding symptoms, such as nocturia, in 75% of patients 3 years after prostate surgery, 25% had little or no improvement and half of these patients had nocturia that worsened as a result.<sup>43</sup>

**Mixed nocturia.** In patients with nocturnal polyuria and diminished nocturnal bladder capacity (elevated index) the predominant cause of nocturia should be assessed. For example, if a patient has a nocturnal bladder capacity index of 0.8 and nocturnal polyuria to the extent that nocturnal urine volume is 75% of 24-hour urine production, treatment of nocturnal polyuria should be prioritized and would be expected to provide a greater benefit to symptomatic nocturia than a strategy to diminish the contribution from low nocturnal bladder capacity. In general, we recommend initial treatment of nocturnal polyuria since it does not involve invasive or potentially irreversible treatment, such as surgical procedures intended to affect obstructive uropathy. We recently reviewed the records of 129 female and 65 male consecutive patients from 17 to 94 years old (mean age 59) with nocturia who were evaluated with a history, voiding diary with day, night and 24-hour voided volume, post-void residual urine and video urodynamic study.<sup>35</sup> Overall, 13 patients (7%) had nocturnal polyuria, 111 (57%) low nocturnal bladder capacity and 70 (36%) mixed nocturia. In addition, 45 patients (23%) also had polyuria. This study confirmed that the etiology of nocturia is multifactorial and in

many instances unrelated to the underlying urological condition, such as BPH, urge or stress incontinence and detrusor instability. Nocturnal overproduction of urine was a significant component of nocturia in 43% of these patients, many of whom also had low nocturnal bladder capacity. Therefore, rational care of the patient with nocturia entails the concept that treatment should be directed at both conditions.

*Symptomatic treatment agents.* Elderly patients with nocturia due to bladder instability have been treated with anticholinergic therapy, such as propantheline, oxybutynin and scopolamine.<sup>102, 103</sup> These agents reduce but do not eliminate the number of nocturnal voids. Side effects include dry mouth, drowsiness, facial flushing and confusion. Patients diagnosed with sleep disorders causing or due to nocturia are commonly treated with hypnotics. Traditionally barbiturates have been used but due to problems of dependence and tolerance, benzodiazepines now are more commonly prescribed and occasionally effective to help some patients resume sleep after awakening.<sup>104</sup>

#### CONCLUSIONS

Nocturia is a poorly reported and infrequently diagnosed condition that causes significant distress to a large number of people. It is among the common reasons for persistent insufficient sleep, which in turn is responsible for psychological and somatic disease. Nocturia may be attributed to nocturnal polyuria and/or diminished nocturnal bladder capacity. Distinction between these conditions is made by a simple arithmetic analysis of a 24-hour voiding diary. Initial treatment should be directed at nocturnal polyuria unless its contribution is minor in comparison to the magnitude of the nocturnal bladder capacity index.

#### APPENDIX 1: CAUSES OF NOCTURNAL POLYURIA

Cause	Reason
Reverse in nocturnal/diurnal urine production	Absence of circadian rhythmicity in arginine vasopressin secretion, solute diuresis mediated by increased atrial natriuretic peptide levels in patients with sleep apnea
Polydipsia	Polyuria, diabetes mellitus/insipidus, excessive fluid intake, especially in evening
Third space loss	Congestive heart failure, venous insufficiency, excessive salt intake, the hypoalbuminemia/nephrotic syndrome
Other	Late evening administration of diuretics

#### APPENDIX 2: COMMON CAUSES OF LOW NOCTURNAL BLADDER CAPACITY

- Infravesical obstruction
- Idiopathic nocturnal detrusor instability
- Neurogenic bladder
- Cystitis: bacterial, interstitial, tuberculous, radiation
- Cancer of bladder, prostate, urethra
- Learned voiding dysfunction
- Anxiety disorders
- Pharmacological: xanthines (theophylline, caffeine),  $\beta$ -blockers
- Bladder calculi
- Ureteral calculi

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