Nocturia and Urgency in Overactive Bladder

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Urgency is the key symptom of the overactive bladder (OAB); indeed, it is the only symptom that the patient must have to be described as having OAB. In 2002 the ICS formulated a consensus definition of OAB as urgency with or without urgency urinary incontinence (UUI), usually with frequency and nocturia, in the absence of local pathological or endocrine factors. The new definitions of OAB and its symptoms are worded on the assumption that the root cause is involuntary detrusor contractions characteristic of detrusor overactivity (DO) [1]. The new definition of urgency only applies to fear of leakage, and this is implicit in the words of the definition ‘sudden compelling desire to pass urine which is difficult to defer.’ Indeed, it is often impossible to defer, and the patient then has UUI.

Therefore, the ICS definition of urgency supersedes the old one, which stated ‘for fear of leakage or pain’ [2]. The ICS argues that the bladder sensation felt by patients with ‘painful bladder syndrome’ is usually described, by such patients, as a discomfort which, as the bladder fills, develops into worsening pain. However, patients with painful bladder syndrome, even the minority with a classic Hunner’s ulcer, rarely leak urine. Patients experience pain, frequency and nocturia but not the cardinal symptoms of OAB, i.e. urgency and UUI.

The new ICS definition of urgency also is at variance with some other definitions, such as the National Institutes of Health (NIH) symptomatic definition of ‘interstitial cystitis’ as ‘frequency, pain and urgency’ [3]. The NIH definition does not differentiate between the powerful desire to void felt by patients with interstitial cystitis, which is driven by pain, and urgency in OAB patients, which is driven by fear of leakage. This confusion in the use of the word urgency is a disservice to patients, as it makes focused management more difficult. It is important that the national and international governmental and professional organizations communicate and agree to use common definitions [4].

Urgency is said to occur without UUI in more than half of patients with OAB. These data come from a USA prevalence study of patients with OAB with and without UUI [5], and a second similar study in Europe to determine the prevalence of OAB (using a definition from before 2002), defined as the presence of frequency, urgency and UUI, either alone or combined, which is presumed to be caused by DO [6]. Using different definitions, results of both surveys indicated that 16% of the population have OAB.

However, when patients say they have urgency, it is difficult to be sure that continent (OAB-dry) patients are describing the same symptom as patients with OAB who have UUI (OAB-UUI). Older clinicians with an interest in OAB and DO recognize the difference between true urgency (for fear of leakage) and a strong or very strong desire to void. If a person is unable to void because of circumstances, e.g. because they are caught in an elevator or in a highway traffic jam, then the normal strong desire to void turns into pain, which can ultimately be as painful as acute retention. This sensation is felt suprapublically. On the other hand, ‘latch key’ urgency, or urgency during hand-washing, which those same older clinicians have experienced, feels different. It is widely held that with true urgency, leakage is considered a possibility if strong pelvic floor contractions are not used, and that the sensation is more urethral. One colleague has catheterized himself and has correlated what he considers true urgency with involuntary detrusor contractions typical of DO.

There is a possibility that the diagnosis of OAB-dry is less secure, as discussed earlier. In turn, this may have implications for the success of OAB treatment, which might be reduced in apparent OAB-dry if the origin of the symptoms is not DO. On the other hand, it also seems likely that in some patients OAB-dry is a mild, or perhaps earlier, form of OAB that will progress with time to OAB-UUI.

Additionally, there are undoubted difficulties in ensuring that urgency as described by the patient is understood objectively rather than subjectively by the clinician, doctor or nurse, who may interpret the symptoms based on his/her imagination or experience. This uncertainty compounds the difficulty of measuring urgency.

The matter becomes more complex if it is considered that true urgency might have causes other than involuntary detrusor contractions. Many will have read Barrington’s description of his second reflex. In the cat, he proposed that when urine enters the posterior urethra it initiates a detrusor contraction [7]. This is theory, not fact. Bladder neck incompetence is seen regularly during video-urodynamics performed to investigate stress urinary incontinence, and Versi et al. [8] showed that half of postmenopausal continent women had an incompetent bladder neck, arguing against Barrington’s finding.

When measuring urgency and bladder sensation one must consider two questions. First, is urgency an all-or-none phenomenon? Second, if not, can urgency be graded by, perhaps, duration and/or severity?

If we assume that true urgency can only be due to an involuntary detrusor contraction, then clinical urodynamic experience would indicate that it is not an all-or-none phenomenon, but is felt to varying degrees, and for varying duration, during DO waves, occurring as the bladder is filled. So how can urgency be assessed? The scales suggested below may help answer this question. As discussed in Tables 1 and 2, urgency may need to be graded by the patient outside the clinical environment or by the patient during urodynamic investigation. Initially, the patient will want to understand how the clinician would like urgency to be assessed. The first step is to give the patient the new ICS definition in ‘layman’s terms, e.g. “When we ask about “urgency” we are asking about a feeling that comes on suddenly, and makes you want to rush to the bathroom because you fear you might leak if you do not go straightaway.”

Currently, we are testing a scale to be used to record every void on a frequency-volume chart (FVC), which is completed by patients before clinic and urodynamic appointments...
(Table 1). Naturally, we define urgency as stated above. During urodynamics, we are testing bladder sensation every 30 s using a 6-point scale (Table 2). In addition, we are testing a bladder-sensation monitor during urodynamic studies. The patient is asked to keep his/her finger on the sensation recorder for the duration of each sensation (Fig. 1).

In a cystometric study, sensation will be correlated to detrusor pressure. The opportunity will be taken to compare the grades of urgency (entered on the FVC for each micturition during the patient’s everyday life) with the sensations experienced during urodynamic testing. It is a fundamental aim of urodynamics to reproduce the patient’s symptoms. Therefore, asking the patient whether or not the symptoms that are felt in everyday life also occur during urodynamic testing is very important. Such testing requires the involvement of a skilled clinician who can make correlations between the patient’s everyday symptoms, their symptoms/sensations during urodynamic testing, and the urodynamic findings.

What of the future? Colleagues in basic science are producing interesting data that raise important questions about the respective roles of the afferent and efferent nerves and neurotransmitter release in the bladder epithelium. This work may complicate our relatively simple or simplistic (depending on one’s perspective) ideas about urgency and UUI. In short, things may get worse (more complicated) before they get better, i.e. before we understand the genesis of urgency and the cause(s) of OAB and DO. This supplement contains important articles that highlight the need for further research on the genesis of OAB symptoms in general and urgency in particular.

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Abbreviations: FVC, frequency-volume chart; DO, detrusor overactivity; OAB, overactive bladder; UUI, urgency urinary incontinence.
Epidemiology of nocturia

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The incidence of nocturia episodes increases with age and is associated with interrupted sleep and distress. There are no large differences in the incidence of nocturia between men and women, but young women tend to have it more frequently than young men, and very old men have it more often than very old women. The International Continence Society has defined nocturia as 'the number of voids recorded during a night’s sleep: each void is preceded and followed by sleep.’ This simple and useful definition should facilitate further epidemiological study of nocturia. Although there are many direct prevalence studies of nocturia, there is a great need for more advanced analytical epidemiological data on risk factors and comorbidity. Clinicians should question patients about nocturia and should consider this symptom in a broader sense than in its traditional association with benign prostatic obstruction in men and incontinence in women. There are several classic studies of nocturia. The nature of future epidemiological research will depend on the resolution of several methodological issues. Further evaluation of nocturia is warranted because of its high incidence among the general adult population.

KEYWORDS
nocturia, lower urinary tract dysfunction

INTRODUCTION

The epidemiological study of nocturia has provided a broad overview of this symptom. In the general adult population, nocturia is a common cause for interrupted sleep and is associated with significant distress [1]. The overall incidence of nocturia tends to increase with age; in those aged 20–80 years, nocturia occurs almost equally in men and women [2]. In addition, there is fair evidence of a relation between nocturia and behavioural and/or environmental conditions, including excessive fluid intake and clinical conditions such as primary sleep disorders, diabetes mellitus, cardiovascular disease, detrusor overactivity, polyuria, lower urinary tract obstruction, stroke and congestive heart failure, and benign prostatic obstruction [1,3].

As opposed to descriptive epidemiology (the simple description of a symptom or disease, i.e. prevalence, incidence, and mortality by person, place and time) analytical epidemiology describes the search for determinants of disease risk. It can be used after experimental or clinical work to investigate the magnitude or prevalence of one or more specific factors. The discovery of factors that confer risk or protection for a particular disease may, in turn, lead to primary or secondary prevention and treatment measures. This report provides an overview of classic epidemiological studies of nocturia, including methodological issues for consideration, and concepts for future investigations to further evaluate this common and distressing symptom.

DEFINITIONS

The definition of a disease is a critical factor in evaluating its epidemiology and the study of nocturia is no exception to this rule. When there are variations in the definitions used in different studies, the assessment of results is confounded. To facilitate more accurate comparison of data, the overall vocabulary used in epidemiological studies should be clearly defined early in the course of such research. Because of the need to control for factors for various purposes, results should include relative risks and statistical calculations rather than simply percentages and distributions.

The ICS has published definitions of the signs, symptoms, urodynamic observations and conditions associated with lower urinary tract function [4]. Nocturia is described as a symptom suggestive of a lower urinary tract dysfunction and is specifically defined as ‘the number of voids recorded during a night’s sleep: each void is preceded and followed by sleep’ [4,5]. This definition has excluded predefined thresholds and terms like ‘bother’ and ‘complaint’ because their use could result in a distortion of the determination of incidence, prevalence, course and risk factors [6].

MEASUREMENTS OF NOCTURIA

For several reasons, the new ICS definition for nocturia is considered a good definition for use in epidemiology studies. First, the definition is relatively simple and can be easily integrated into large population-based studies. In addition, patient questions can be phrased to elicit straightforward answers, such as summation of nocturnal episodes, yes/no responses and compilation of the number of voids during the night’s sleep. However, caution is advised because although these types of questions can be answered simply, the respondent’s interpretation of the queries may remain a source of difficulty. Thus, variability in the data collected can be an issue. Essentially, the patient’s mean value is being captured, but it is not always clear if the mean value the patient is reporting is from the last week, last month or an occasion months ago that he/she wants to document. By their very nature, these types of questions are subject to recall bias, although relative to other conditions, it is likely to be small in studies of nocturia.

One strategy to combat recall bias is to capture episodes of nocturia as continuous variables that are grouped at baseline and during the study into categories such as ‘0’, ‘1–2’, ‘2–3’, etc. Episodes of nocturia are generally thought of as a static number; however, the actual number of nocturia episodes often varies within one patient. One issue when measuring nocturia episodes is that techniques do not take into account variations in occurrence. Another important consideration when questioning patients about nocturia is whether they have a true understanding of the reason for their awakening, i.e. urgency or another factor altogether, such as taking a painkiller.
Epidemiology of Nocturia

The concise and simple ICS definition of nocturia provides an excellent starting point for gathering descriptive statistical data. A useable definition should provide a reliable and valid measure that can serve as a solid foundation for a given study. Descriptive epidemiology studies in nocturia therefore can be improved by several mechanisms. Researchers should be encouraged to report their data in a fashion that stratifies results by gender and age. A well-conducted study should cover a predefined age span to control for age effects. Some measure of bother, quality of life, or impact on daily living, in addition to other symptoms, should be recorded to facilitate a more clinical approach to the issue of nocturia. Furthermore, the number of potential patients with nocturia cannot be projected based on simple descriptive epidemiological data. There is no guarantee that a subject who responds to an epidemiological study will seek medical attention for the problem being investigated. Finally, symptoms that are severe should not be assumed to be frequent and vice versa.

TABLE 1 Various aspects of sleep in relation to the number of nocturnal voiding episodes in women aged 40–64 years (values are %). Adapted from Asplund et al. [8]

<table>
<thead>
<tr>
<th>Aspect</th>
<th>Nocturnal voiding episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>My sleep is poorer than it was 5 years ago:</td>
<td>17 29 39 58 27 &lt;0.0001</td>
</tr>
<tr>
<td>I sleep too little every night:</td>
<td>9 16 25 38 15 &lt;0.0001</td>
</tr>
<tr>
<td>I lie awake for &gt;30 min before going to sleep at night:</td>
<td>40 51 64 65 49 &lt;0.0001</td>
</tr>
<tr>
<td>I often have nightmares:</td>
<td>5 9 18 27 9 &lt;0.0001</td>
</tr>
</tbody>
</table>

FIG. 1. Differences in prevalence of nocturia by gender and age (N = 2506). Men/women ‘1’ denotes one episode of nocturia/night, men/women 2+ denotes ≥2 episodes/night. Reprinted with permission from Van Dijk et al. [5].

FIG. 2. Percentage of nocturnal voiding episodes in women aged 40–64 years (N = 3669). Reprinted with permission from Asplund et al. [8].

DESCRIPTIVE EPIDEMIOLOGY FOR NOCTURIA

In 2002, Van Dijk et al. [3] published the results of a population-based survey designed to estimate the prevalence of nocturia in a representative sample of the adult population in the Netherlands. In all, 4721 calls to potential participants were made and 2506 subjects (53%) agreed to participate. Because the sample included slightly more women and older subjects, the results were standardized for gender and age to represent the entire Dutch population. The questionnaire consisted of 15 queries including referral to nocturia, age, gender, general health status, use of medications, and sleep disturbances. Nocturia was measured using back-translated questions from the Bristol Lower Urinary Tract Symptoms questionnaire, an instrument with proven psychometric validity and reliability [7].

A clear association between perceived health status and nocturia was discovered. Respondents who perceived themselves to be in excellent health had the lowest prevalence of nocturia (5%), whereas those with a poor-to-moderate perception of health reported a prevalence of 34%. In addition, the overall prevalence of nocturia was higher in women (16%) than in men (9%); P < 0.001. There was a strong association between age and nocturia (Spearman’s correlation 0.37; P < 0.001; Fig. 1). The highest prevalence of nocturia was found in the oldest group (37%; aged ≥75 years), whereas the lowest prevalence was in the youngest group (5%; aged 18–34 years). The prevalence of nocturia was 37% for both men and women in the oldest group, while the largest difference between the genders was in the group aged 55–74 years (22% for men vs. 43% for women). In conclusion, the data suggest that women start to develop nocturia at a younger age than do men.

A questionnaire survey was conducted by Asplund and Åberg [8] in 3669 randomly selected women aged 40–64 years (61% response rate) in Sweden to assess nocturnal micturition patterns in relation to sleep. The questionnaire used in their study was designed to capture the number of nocturnal voiding episodes, as well as the general state of health, occurrence of diseases and symptoms, various habits and behaviours, and qualitative and quantitative questions about sleep. Data were analysed in relation to the number of nocturnal voiding episodes and respondents were grouped by this number. Women who reported an interval number of nocturia episodes (such as one to two) were allocated to the group with the fewest (in this case, to one episode).

The percentage of women reporting one nocturnal voiding episode was greater for the oldest group (62.4%; aged 60–64 years) than for the youngest group studied (44.6%; aged 40–44 years; Fig. 2). This study showed a large difference between the incidence of one nocturnal voiding episode (=50%) and two (=10%) or three (=5%) episodes. Deterioration in sleep was more closely associated with increased nocturnal micturition than with increasing age. Reports of sleeping too little every night, as well as nightmares, were four times more likely to occur in women with ≥3 voiding episodes/night than in those with none (Table 1). The finding that nocturnal voiding was associated with troubled sleep was more pronounced in women aged 45–49 years (R² = 0.158; P < 0.0001) and least pronounced in those aged 60–64 years (R² = 0.111; P < 0.0001). Frequent nocturia was associated with...
increased sleep disorders, poorer quality of sleep and increased fatigue during the daytime.

As part of a comprehensive health study, a self-administered questionnaire was used from 1995 to 1997 in men aged ≥20 years living in a county in Norway, by Seim et al. [9]. The instrument used included variables on demographics, lifestyle factors, current medications and urinary history; the last included recording nocturia episodes and prostatic enlargement. Three different definitions were used to calculate prevalence estimates for nocturia: having to get up to void ≥1, ≥2 or ≥3 times/night.

Of the 30 556 men who returned the questionnaire, 75.9% (23 220) answered questions about nocturia. The prevalence of nocturia increased with age, regardless of the definition used (Fig. 3). As in the previous study [8], there was a large difference between the prevalence of men who reported one nocturia episode and those who reported two or more episodes; however, differences in the prevalence of those who reported two or three episodes were not as marked. In addition to age, prostatic enlargement, use of antihypertensive medications and increased waist/hip ratio were independent correlates of nocturia in men. The data suggest that nocturia is prevalent in men and the prevalence increases with advanced age.

**DISCUSSION**

Descriptive epidemiological data on nocturia indicate that this symptom increases with age and the steepest increase is in older groups (>65 years). There were no large differences in the prevalence of nocturia between men and women; however, there is a tendency for young women to have this symptom more often than young men, and for very old men to have it more often than very old women. Typical ranges for ≥2 nocturia episodes/night are 5–15% for those aged 20–50 years, 20–30% for those aged 50–70 years and 10–50% for those aged ≥70 years [3,8,9].

**ANALYTICAL EPIDEMIOLOGY FOR NOCTURIA**

There are many simple prevalence studies of nocturia; there is a need for more advanced epidemiological analysis of risk factors and comorbidity, using multivariate techniques to further elucidate questions regarding cofactors and predictors for nocturia. Contemporary analytical epidemiology studies in nocturia should be powered to compare age groups and some important subgroups. In addition, appropriate statistics such as confidence intervals need to be included with the results to improve the applicability of findings. In more advanced analyses, confounders should be controlled by the use of stratification and multivariate techniques to obtain a clearer picture of cofactors and predictors. Because there are few data on the distribution of several risk factors and attributable risk of factors in the population at large, special attention should be focused on these areas in future studies.

When evaluating analytical epidemiological data it is important to define ‘normal’ and to distinguish between perceptions of symptoms and clinical entities. To maintain a more clinical approach, analytical measures should be combined with a secondary measure, such as bother, quality of life, or a clinically relevant symptom score, and/or should be associated with a risk or complication in a valid fashion. Finally, epidemiological data are prone to being misused or abused because associations often have been misinterpreted as causes. This dilemma is often described as the ‘chicken or the egg’ syndrome.

Nocturia appears to be a predictor of unfavourable consequences for sleep quality and quantity [8]. Although this explanation of the relation between nocturia episodes and disturbances in sleep appears to be logical, it is possible that the basic mechanism is entirely different [8]. Insomnia secondary to nocturia is an important consequence that should be recognized by primary-care providers, particularly in elderly patients who are prone to have a poorer quality of sleep than are younger ones [10,11]. As the number of nocturia episodes per night increases, so do the negative effects on sleep [12]. Further study of the different phases of sleep, and the different levels of arousal when nocturic episodes occur, should be considered in the evaluation of this symptom for the purposes of analytical epidemiological study [11]. For example, patients could be asked whether they wanted to return to sleep after waking up to void. The case of a person who wakes up at 04.00 hours because of the need to void, and then goes back to bed but is unable to return to sleep, would not meet the strict ICS definition of nocturia. Such a case may have quality-of-life implications whose relation to nocturia would not be captured unless the deficiency was specifically addressed in the study design.

**CONCLUSION**

In the past, the use of different definitions and measurements has been a major problem in epidemiological research of LUTS, including nocturia. Even data collected from simple questions using a seemingly straightforward definition of nocturia can become complex, particularly when conducting in-depth research about comorbidities. The ICS definition of nocturia appears to be useful and simple, and should help identify people with nocturia in large population-based studies. In addition, effective tools for questioning patients about nocturia are available [7].

It is well established that nocturia is associated with ageing. In general, the incidence and severity of nocturia increases consistently from early adolescence to senescence, and the proportion of people who consider nocturia to be a problem tends to increase as the frequency of nocturia increases [2,3]. Most people who have reported nocturia in epidemiological studies have also said that they have not sought treatment [13]. Clinicians should query patients about nocturia and should consider this symptom in a broader sense than in its conventional association with benign prostatic obstruction in men and incontinence in women.

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Classification of nocturia in the adult and elderly patient: a review of clinical criteria and selected literature

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Nocturia increases with age and significantly affects quality of life in both men and women. Attempts to determine the pathogenesis of nocturia have been based on frequency-volume charts, and three types of nocturia have been identified: low voided volume (previously termed low bladder capacity), nocturnal polyuria, and mixed origin. Validated clinical criteria based on frequency-volume data allow the type of nocturia to be specified using two threshold values, i.e. largest voided volume/body weight ratio <4 mL/kg for low voided volume; and nocturnal urinary output/body weight ratio >10 mL/kg for nocturnal polyuria. The utility of these thresholds was validated in a study of elderly patients with two or more nocturia episodes/night. Two other studies have improved the understanding of the epidemiology of nocturia. The first showed that in men and women, increased incidence with age was greater for nocturia than for the six other common lower urinary tract symptoms. The second study suggested that prostate changes in men (particularly bladder outlet obstruction caused by benign prostatic hyperplasia, which has been considered to be a major cause of nocturia) appear to play a relatively small role in the development of nocturia; the correlation was based on overall symptom score for seven common urological symptoms. Nocturia should thus be treated independently of other lower urinary tract symptoms, especially in men. The application of valid diagnostic criteria to differentiate the underlying cause of nocturia should help lead to more appropriate and effective management of this pervasive problem.

KEYWORDS
nocturia, elderly, low bladder capacity, low voided volume, nocturnal polyuria, detrusor overactivity, benign prostatic obstruction

INTRODUCTION

The ICS definition of nocturia is the complaint that a person has to wake once or more at night to void [1]. Nocturia, or nocturnal waking to void, has been reported in up to 58–90% of people aged >50 years [1,2], with the prevalence increasing with age [1,3–5]. This condition can significantly impair the patient’s perception of their well being [6] and often warrants treatment, especially when the patient must wake twice or more per night [7,8]. Weiss et al. [7] reported that 83% of women with two or more nocturia episodes/night considered the problem to be bothersome and 37% considered it to be a serious problem, whereas only 22% of those with 1–2 episodes/night considered it to be problematic.

Nocturia has only recently been recognized as a clinical entity [2] and its cause remains unclear in a significant number of patients [7]. However, it has been correctly correlated with nocturnal polyuria [7,9] and low voided volume (previously termed low bladder capacity) that is most probably associated with detrusor overactivity (DO) [2,7,9]. Nocturia has also been considered to be a typical symptom of benign prostatic obstruction (BPO).

The appropriate treatment for nocturia depends on correctly recognizing its pathogenic mechanisms [7], which can be accomplished using the clinically validated, easily applicable criteria for diagnostic classification of nocturia that are discussed in this review.

CLASSIFYING NOCTURIA

The probable mechanical causes of nocturia in the elderly are impaired contraction of the detrusor muscle [2,9,10] with diminished nocturnal voided volume and endocrinological changes leading to polyuria and nocturnal polyuria [2,9]. Diagnostic classification systems for nocturia should identify these entities clearly to help direct treatment. Ideal methods for classifying the cause or type of nocturia should be easily applicable in a clinical setting and take into account gender-linked differences, such as body weight (BW) [11]. The following sections summarize some of the work that has been carried out to develop validated criteria.

OBTAINING DATA: THE FREQUENCY–VOLUME CHART (FVC)

The standard tool for initial diagnosis of nocturia is the FVC, a specific urodynamic tool that records fluid intake and urine output over a 24-h period for ≥1 day [2,12–16]. This patient-maintained chart generates objective information on the total number of voids/24 h, the distribution of daytime and nocturnal voids, and individual and cumulative voided volumes [12]. Kassis and Schick [15] noted that information obtained by the FVC is invaluable for understanding subjective urinary symptoms.

According to the Standardisation Sub-committee of the ICS, nocturia can be described and quantified by three values from the FVC; the 24-h (total) urinary output ($U_t$), nocturnal urinary output ($U_n$), and largest voided volume ($V_L$; previously termed functional bladder capacity) [2]. However, the classification of nocturia into types or causes necessitates using additional FV variables such as those included in a study by Saito et al. [13], i.e. 24-h, waking, and $U_w$; 24-h, daytime and nocturnal frequency of voiding; and 24-h, daytime and nocturnal voided volume. These investigators addressed the causes of daytime and nocturnal urinary frequency in 215 patients (66 men and 149 women), aged 16–84 years, divided into elderly (aged > 65) and adult (aged ≤ 65) groups [13]. To ascertain the causes of frequency, the FV data were supplemented with a detailed medical history, physical examination with or without a free-flow
IDENTIFYING CAUSES OF NOCTURIA

In their study of urinary frequency, Saito et al. [13] found that in their study group the 85 elderly patients were more likely than the 130 younger patients to have problems leading to nocturia rather than daytime frequency (defined as ≥10 voids during waking hours, with a normal voided volume and no incidence of nocturia) [13]. In comparison with the younger patients, the elderly had a lower daytime urine output and greater U<sub>N</sub>, and more frequent and smaller nocturnal voids (Table 1) [13]. The most common cause of urinary frequency in the elderly was found to be nocturnal polyuria (37%), followed by DO (34%); the remaining cases were attributed to increased fluid intake (14%), normal micturition (7%), undefined causes (6%), and frequency (2%) [13].

Results of a population-based survey study [1] to obtain more reliable epidemiological data on LUTS in patients in Japan showed that prevalence increased with age and LUTS were generally more common in men. The two most common symptoms among the 4570 patients aged ≥40 years were nocturia (364 out of 85 and 130, respectively) [13]. In their study of urinary frequency, Saito et al. [13] found that in their study group the 85 elderly patients were more likely than the 130 younger patients to have problems leading to nocturia rather than daytime frequency (defined as ≥10 voids during waking hours, with a normal voided volume and no incidence of nocturia) [13]. In comparison with the younger patients, the elderly had a lower daytime urine output and greater U<sub>N</sub>, and more frequent and smaller nocturnal voids (Table 1) [13]. The most common cause of urinary frequency in the elderly was found to be nocturnal polyuria (37%), followed by DO (34%); the remaining cases were attributed to increased fluid intake (14%), normal micturition (7%), undefined causes (6%), and frequency (2%) [13].

Three types of nocturia were delineated: pure nocturnal polyuria, low voided volume, and mixed (nocturnal polyuria + low voided volume). Polyuria was considered separately, because it increases 24-h urine production [7,9]. To confirm a diagnosis of nocturia and distinguish among the three types, the investigators proposed the following definitions based on FV values.

To identify low voided volume and nocturnal DO, U<sub>N</sub> is divided by V<sub>T</sub> to produce a value for the predicted nightly void [7]. DO is present when the difference between the actual and predicted numbers of nightly voids is greater than zero [7].

Nocturnal polyuria is present when U<sub>N</sub> is >35% of U<sub>T</sub> [7,13], but this percentage was not critically defined. The ICS definition of nocturnal polyuria is a nocturnal urine volume of ≥20–30% of total 24-h urine volume (age dependent) [1].

It was postulated that applying these definitions may help to stratify patients and direct appropriate treatment, such as timing of diuretics, evening fluid restriction, vasopressin administration [7] and antimuscarinic therapy [17]. However, these definitions have not been clinically validated.

DEVELOPING VALID DIAGNOSTIC CRITERIA

To further clarify the types and causes of nocturia and to rectify the lack of validated, clinically practical diagnostic criteria based on FVCs, two multicentre studies were designed, the first to define criteria threshold values and the second to validate these criteria [18].

STUDY 1: DEFINING DIAGNOSTIC MARKERS AND VALUES

The first study, to determine markers and threshold values for nocturia, included 67 patients aged 24–89 years (35 men, mean age 58.2 years; 32 women, mean age 61.1 years) who were admitted to ambulatory urological study, and cystometry (the only invasive measure), which was necessary in only 16% of patients [13].
wards in five Japanese medical institutions and had no evidence of voiding disorders [18]. Patients were stratified into five age groups (20–49, 50–59, 60–69, 70–79 and 80–89 years), with five or more subjects/group. All patients completed a 24-h FVC and completed the IPSS [18]. Basic FV data included frequency of voiding (24 h, daytime and nocturnal), voided volume/void (largest, V₇, and average, V₅), and urinary output (24 h, U₄ and U₅). There was no significant difference between men and women for any demographic features except mean BW (60.4 and 53.0 kg, respectively), mean voiding episodes/night (1.2 and 1.1, respectively) and IPSS (5.6 and 5.4, respectively). The mean V₇ was significantly greater in men than in women (P = 0.028), and mean V₅ and V₆ were greater in men than in women (although not significantly). However, the differences did not persist after data were corrected for BW (Table 2) [18].

Analysis of the corrected data showed significant correlations between age and nocturnal urinary frequency, and for both age and nocturnal urinary frequency with IPSS, quality-of-life index, decreased maximum flow rate, and postvoid residual volume, independent of gender of the patient. Both age and nocturnal urinary frequency also correlated significantly with all frequency and voided-volume values. Nocturnal, but not total, urine production values correlated with nocturnal frequency, but no urine production value correlated with age (Table 3) [18].

In a linear regression model, only U₇/V₇ was highly predictive of nocturnal urinary frequency (r² = 0.67). This result suggested that urinary output and voided volume are two independent domains contributing to nocturia. However, if the model were used as a criterion for diagnosis it would be uninformative about the relative role of each domain [18]. Linear regression was therefore used to construct a model that would generate two separate thresholds, one for each domain. The model of V₅/BW and U₅/BW, being less dependent on individual body size, was selected (predictive value r² = 0.57) [18].

Thresholds defined for both highly predictive models were set close to the worst quartile and one SD worse than the mean. In the first model, nocturia was defined as V₅/BW < 4 mL/kg and U₅/BW > 10 mL/kg. If the two primary causes of nocturia are considered to be nocturnal polyuria and low voided volume,
The value that includes the single largest voided volume ($V_L/BW$) should provide an indication of bladder capacity, and the value that includes the nightly urinary output ($U_N/BW$) should reflect nocturnal polyuria. In the alternative model, nocturia was considered present with $U_N/V_L > 2.5$ \[18\]. Adjustment by $BW$ is important when the criteria are used for populations with differing body size, i.e. for men and women or for Asians and Caucasians.

**STUDY 2: VALIDATION OF CRITERIA**

The chosen criteria were validated in a study of patients aged >60 years (20 men, mean age 72.3 years; 19 women, mean age 73.8 years) who reported two or more nocturnal voids \[18\]. Except for the age of the patients and number of nightly voids, conditions were similar to those in the first study; patients were drawn from the ambulatory urology wards of the same five centres, where they had been admitted for problems unrelated to lower urinary tract dysfunction. Each patient completed a 24-h FVC; all FVCs were analysed for the same data as in the earlier study, and patients were classified into two groups, i.e. two voids/night and 3–4 voids/night. The first study was used to supply reference values for the third group representing those with 0–1 nightly void \[18\].

The two main criteria of $V_L/BW < 4 \text{ mL/kg}$ and $U_N/BW > 10 \text{ mL/kg}$, and the supplemental criterion of $U_N/V_L > 2.5$, correlated well with the number of voids/night. In patients with 3–4 nightly voids, all mean values for $V_L/BW$, $U_N/BW$, and $U_N/V_L$ met the criteria for nocturia, and in reference subjects with one void or less, no mean values met the criteria. In the group with two voids/night only the mean values for $U_N/BW$ met that criterion (Table 4) \[18\].

From the criteria, pathogenic trends could be identified when the thresholds were used to classify subjects into four groups: no abnormality, nocturia associated with low voided volume, nocturia associated with nocturnal polyuria, and nocturia with both low voided volume and nocturnal polyuria \[18\]. Half of the group with one or less void/night had no abnormality. Every patient with 3–4 voids/night had one or both of the abnormalities, and low voided volume plus nocturnal polyuria was found only in this group (Fig. 1) \[18\]. A retrospective application of the criteria to a large group of outpatients...
from an unpublished study of nocturia showed a similar distribution of low voided volume and nocturnal polyuria (Fig. 2) [19].

POSITIONING NOCTURIA: RELATION TO AGE AND LUTS SUGGESTIVE OF BPO

AGE AND BLADDER PATHOLOGY IN NOCTURIA

The strong correlation of age with nocturia was shown in a study including 269 subjectively asymptomatic patients aged 32–83 years (168 men, mean age 56.1 years; 101 women, mean age 68.1 years) presenting to a urological outpatient clinic. All patients completed a self-administered questionnaire in which they were asked about the presence and frequency of seven symptoms, i.e. hesitancy, protraction (prolongation of urination), weak stream, terminal dribbling, urgency, daily frequency and nocturia [20]. The patients were stratified into five age categories (≤49, 50–59, 60–69, 70–79 and 80–84 years) [20], and the severity of each symptom was subjectively scored from 0 to 2; a score ≥1 was considered symptomatic [20].

Overall, urinary symptoms were more common in men; symptoms occurred in 38–77% of men vs 17–58% of women, aged 80–84 years. There was a higher prevalence of symptoms in men in all age categories [20]. All symptoms increased gradually with age in both men and women (Fig. 3a,b). Nocturia had the most dramatic rise, increasing by 57% in men and by 50% in women from age ≤49 to ≥80 years [20]. The second most dramatic rise occurred in weak stream, which increased by 47% in men and by 25% in women from age ≤49 to ≥80 years. Minimal increases with age were present in only two symptoms; terminal dribbling in women (+4%) and protraction in men (+1%) [20].

NOCTURIA AND BPO: A REAPPRAISAL

In men, increasing age is associated with a corresponding increase in BPO [4,8]. Nocturia, like other symptoms, has been presumed to occur as the result of BOO from BPO [4,8]. Surgery for BPO, as well as other prostate-directed treatments, is often recommended to alleviate nocturia and the six other IPSS symptoms [8,21]. However, surgery as a treatment for nocturia often produces ineffective results when BPO is a concomitant ailment [21].

FIG. 3. Age-related increases in urinary symptoms in (a) men and (b) women. Frequencies of symptoms that generated a self-rated severity score of ≥1 are shown; values in parentheses show changes in percentage from age ≤49 to 80 to 84 years. In men, nocturia was the symptom with the greatest age-related increase in frequency, although weak stream was the most frequent complaint for all age groups. In women, nocturia was the symptom that both occurred most frequently in patients aged ≥70 years and that had the greatest age-related increase in frequency. Symptoms that changed the least with age in women were protraction, terminal dribbling and hesitancy. Adapted from Homma et al. [20].
Recent data have helped to clarify that nocturia, in particular, may be an age-associated rather than a BPO-associated symptom, and thus should be managed separately. The distinctiveness of nocturia from other LUTS/BPO symptoms was supported by a retrospective analysis of records of patients who were treated for BPO [11]. The study used the IPSS to determine how nocturia correlates with overall IPSS, age of patients and surgical relief of BPO [11], and included 219 consecutive patients (mean age 69.1 years) treated in the urology department of a teaching hospital in Japan for LUTS suggestive of BPO; all patients completed the IPSS. Exclusion criteria included prostate cancer, bladder tumour or stone, urethral stricture, and neurogenic bladder dysfunction [11]. Patients were divided into two groups by age; <70 years (114; mean age 63.6 years) and ≥70 years (105; mean age 75.1 years), and the IPSS was obtained at baseline and after surgical treatments. Results from the study population were compared with those of a general-population control group of 403 subjects aged 60–79 years (mean 69.4) drawn from an epidemiological study [11,19]. Pearson’s correlation and Cronbach’s $\alpha$ were used to assess score validity and internal consistency [11].

Nocturia correlated less closely with the total IPSS than did any other symptom (Table 5); $r = 0.56$ for nocturia vs 0.60–0.72 for other symptoms, but the seven symptom scores of the IPSS appeared positively correlated with each other and were thus internally consistent ($r = 0.12–0.61$; $\alpha = 0.80$) [11]. Treatment to relieve BPO had less effect on nocturia than on any other symptom, and the mean score after treatment was lower for nocturia than for any other symptom (0.70 vs 0.73–0.77; Table 5). Improvement after treatment, as shown by the change in score, was also smallest for nocturia ($-0.9$ vs $-1.34$ to $-2.3$; Table 6). However, changes after treatment in symptom scores correlated positively and were internally consistent ($r = 0.40–0.60$; $\alpha = 0.87$) [11]. Finally, a standard response mean (score change divided by SD) was calculated to assess the responsiveness of the change in scores. As with other values, the size of the standard response mean remained smallest for nocturia in the total population ($-0.61$ vs $-0.67$ to $-1.11$); the value for nocturia was also the smallest in three of the four subgroups (Table 6) [11].

### Table 6

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean (SD)</th>
<th>Age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>&lt;70</td>
</tr>
<tr>
<td>N</td>
<td>219</td>
<td>114</td>
</tr>
<tr>
<td>Incomplete emptying</td>
<td>$-2.0(1.8)$</td>
<td>$-2.2$</td>
</tr>
<tr>
<td>Frequency</td>
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<td>$-1.6$</td>
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<tr>
<td>Intermittency</td>
<td>$-1.5 (2.0)$</td>
<td>$-1.7$</td>
</tr>
<tr>
<td>Urgency</td>
<td>$-1.4 (2.0)$</td>
<td>$-1.3$</td>
</tr>
<tr>
<td>Weak stream</td>
<td>$-2.3 (2.1)$</td>
<td>$-2.4$</td>
</tr>
<tr>
<td>Hesitancy</td>
<td>$-1.6 (2.1)$</td>
<td>$-1.7$</td>
</tr>
<tr>
<td>Nocturia</td>
<td>$-0.9 (1.5)$</td>
<td>$-1.0$</td>
</tr>
</tbody>
</table>

**Standard response mean**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean (SD)</th>
<th>Age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>&lt;70</td>
</tr>
<tr>
<td>Incomplete emptying</td>
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<tr>
<td>Frequency</td>
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<tr>
<td>Intermittency</td>
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<td>Urgency</td>
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<tr>
<td>Weak stream</td>
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<td>$-1.13$</td>
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<tr>
<td>Hesitancy</td>
<td>$-0.77$</td>
<td>$-0.82$</td>
</tr>
<tr>
<td>Nocturia</td>
<td>$-0.61$</td>
<td>$-0.60$</td>
</tr>
</tbody>
</table>

The standard response mean was calculated by dividing the change in score by the SD, to assess the responsiveness of each IPSS. Adapted from Homma et al. [18].

**FIG. 4.** Application of validated nocturia criteria in reference and study groups with treated BPO. The results are divided according to treatment prostate volume: <20 mL (120 men), 20–40 mL (41) and >40 mL (62). Note that presence and absence of nocturia appear to be independent of prostate size. LVV = low voided volume; NP = nocturnal polyuria.
An unpublished analysis emphasized the correlation of nocturia with age rather than with BPO. Some individuals of the control and treatment study populations [11] had recorded a FVC. They were classified into three groups according to prostate volume (<20, 120 men; 20–40, 41; and >40 mL, 62) and the previously described validated criteria [11] used to diagnose nocturia and identify the pathogenesis of this symptom. The results showed that the presence of nocturia was consistent in all three subgroups, independent of prostate volume (Fig. 4).

CONCLUSIONS

An understanding of how to manage the pervasive problem of nocturia is becoming clearer. The causes of this condition are now well understood, and this has enabled the establishment of validated criteria for use in clinical practice to differentiate the three distinct types of nocturia [11]. The nature of nocturia has been further illuminated by data that show the relative importance of age [1,20] and relative unimportance of BPO [11] in the development of this symptom, which suggests that the problem is best treated independently of other LUTS, especially in men. These advances should help to provide more appropriate and effective management of nocturia.

REFERENCES


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Abbreviations: FVC, frequency-volume chart; BW, body weight; LVV, low voided volume; NP, nocturnal polyuria; UNV, nocturnal urinary output; UI, 24-h urinary output; VMS, average voided volume; VMax, largest voided volume; BPO, benign prostatic obstruction; DO, detrusor overactivity.
Nocturia in relation to sleep, health, and medical treatment in the elderly

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Nocturia is a common condition in the elderly that profoundly influences general health and quality of life. It appears to predict a higher risk of death. One consequence of nocturia is sleep deterioration, with increased daytime sleepiness and loss of energy and activity. Accidents, e.g. falls, are increased both at night and during the day in elderly persons with nocturia. Nocturia is caused by nocturnal polyuria, reduced voided volumes, or a combination of the two. Nocturnal polyuria can be caused by numerous diseases, e.g. diabetes insipidus, diabetes mellitus, congestive heart failure, and sleep apnoea. A disorder of the vasopressin system, with very low or undetectable vasopressin levels at night, is manifested as an increased nocturnal urine output, which in the most extreme cases reaches 85% of the 24-h diuresis: the prevalence of low or undetectable vasopressin levels at night has been estimated to be 3–4% in those aged ≥65 years. Treatment of nocturia may include avoiding excessive fluid intake and use of diuretic medication in the afternoon rather than the morning, oral desmopressin at bedtime in cases of nocturnal polyuria, and antimuscarinic agents in the case of overactive bladder or impaired storage capacity of the bladder.

DEFINITION OF NOCTURIA

A standardization of urological terms was adopted by the ICS in 2002 [15]; in accordance with the new terminology, nocturia is defined as ‘waking once or more at night to urinate’ [15]. Thus the term nocturia, in contrast to the definition commonly used before 2002 (≥2 nocturnal voids) is not restricted to any particular number of nocturnal voids.

NOCTURIA AND MORTALITY

The relation between nocturia, sleep, and different diseases and symptoms have been investigated in an extensive questionnaire survey in northern Sweden. Data from >6000 elderly men and women were collected. After 4.5 years, data on deaths were extracted from the National Central Bureau of Statistics in Stockholm [4]. The overall death rate during the study period was doubled in both men and women with ≥3 nocturnal voids than in those with ≤2 such episodes (Fig. 1) [4]. The difference became significant in men after 2 years, but in women it did not reach a clearly significant level until the study ended, probably as a result of there being few cases. The difference in death rate remained after age, cardiac diseases, diabetes mellitus and stroke had been taken into account.

No single cause of death could explain the excess mortality; there were relatively few people who died from each of the different causes, but there were some symptoms that...
were more prevalent in people who had ≥3 nocturnal voids at the start of the study and who died during the study period than in the group with ≤2 nocturnal voids. In the former group, giddiness and poor balance in the daytime were about twice as common in both men and women, and dry mouth, a consequence of negative fluid balance, was also more common in women.

Individuals who had ≥3 nocturnal voids had also been more troubled by too little sleep, a feeling of not being well-rested in the morning, and by nightmares. Nocturnal drinking was also more common in this group. The habit of nocturnal drinking was noted in only 2–3% of individuals without nocturia. Giddiness when getting up and passing of large amounts of urine were also more common (Fig. 2). These data indicate that elderly persons with nocturia have a greater risk of death, partly as a consequence of injuries and other complications resulting from falls.

NOCTURIA IN RELATION TO HEALTH AND SOMATIC DISEASES

Self-reported health impairment is more prevalent among elderly people with nocturia than among those without [1]. It could be suspected that certain diseases and some kinds of medical treatments may contribute to the occurrence of nocturia. In another report on the survey among elderly men and women in northern Sweden, poor health was reported by 14.7% of the men ≤2 nocturnal voids and by 29.6% of the men with ≥3 nocturnal voids (P < 0.001); the corresponding frequencies in women were 17.4% and 39.9%, respectively (P < 0.001). In a multivariate logistic model, the following significant independent correlates of having ≥3 nocturnal micturitions (vs ≤2) were: age 70–79 years vs <70 years (odds ratio, OR, 1.7; 95% CI, 1.3–2.2); age ≥80 years vs <70 years (1.9, 1.3–2.5); poor sleep vs good sleep (2.6, 2.1–3.2); sequelae after stroke (2.0, 1.1–3.6); irregular heart beats (1.6, 1.2–2.1); and diabetes (1.5, 1.1–2.3). Gender, spasmodic chest pain and snoring were all deleted by the logistic model [16].

There was about a doubling in the occurrence of ≥3 nocturnal voids in elderly men and women with diabetes than in those without [16]. An interesting finding in that study was that diabetes per se was not associated with more nocturnal voids. The whole increase was attributed to the population of women on oral antidiabetic medication. Good control of the diabetic state is accompanied by a reduction in nocturia [17]. Treatment of diabetes in the elderly often begins with diet and exercise, and oral antidiabetic agents are added later. Insulin is often introduced as the last option, when the diabetes is out of control [18]. The increase in the frequency of nocturia among orally treated women may reflect poor glucose control in this group.

Dryness of the mucous membranes of the eyes and mouth is a common complaint in the elderly. In a recent study it was found that 14% of elderly men and 21.7% (P < 0.0001) of elderly women were troubled by dry eyes, and 25% of the men and 36% (P < 0.0001) of the women complained of dry mouth [19]. Nocturia was associated with a significant increase in the occurrence of dry eyes and dry mouth. Increased nocturnal voiding was associated with increased dryness of the eyes and mouth in both men and women. Both dry eyes and dry mouth were more common in women than in men in the groups with different patterns of nocturnal voiding [19].

Nocturia in the elderly is also associated with an increase in several nocturnal symptoms: feeling cold and sweating, which are common symptoms associated with sleep impairment; nightmares, which are believed to reflect disturbances in sleep structure; and increased thirst and drinking, leg tingling, and muscle cramps, which may be caused by fluid or electrolyte imbalances. The prevalence rate of all these symptoms increases in parallel with more nocturnal voids [1].

AGE-RELATED DEVELOPMENT OF NOCTURIA

The frequency of nocturia increases with age in both men and women [20,21]. Sommer et al. [22,23] found that the percentage reporting ≥3 voiding episodes at night increased in both males and females from adolescence (0%) to 60–70 years old (11%).

Among men with difficulty in emptying their bladder because of prostatic obstruction there is a greater occurrence of nocturia. Elderly men with nocturia have shown a greater probability of having a TURP, because their nocturia has been suspected to be linked to prostate obstruction [24]. Persistence of nocturia after TURP in otherwise healthy patients is often caused by an increased urine production at night [25].

DEVELOPMENT OF THE 24-h DIURESIS RHYTHM

In the neonate, diuresis does not differ at different times of the 24-h period. A diuresis pattern develops during the first years of life, with excretion of large amounts of urine in
The occurrence of primary childhood enuresis is to some extent caused by hereditary mechanisms. The propensity for this condition is usually well recognized in certain affected families [28].

The total 24-h urine output in adult men and women is ≈1600 (±300) mL and does not change substantially with increasing age [29–31]. In contrast, the distribution of the urine output during the 24-h period changes considerably [31,32]. At the age of 30 years, twice as much urine is produced in the daytime as at night, whereas in those aged >65 years the urine output is somewhat higher at night than during the day [31]. In certain cases with pronounced diuresis at night, the nocturnal part of the 24-h urine output exceeds 85% [29].

The relation between voiding pattern and diuresis

In one study the urine output and voiding frequency in elderly people were investigated, with 41% men and a mean (±SD) age of all subjects of 71.6 (±6.1) years [30]. The urine volume and the number of voiding episodes were recorded in 12-h periods from 08.00 to 20.00 hours, and from 20.00 to 08.00 hours, for 72 h. In the whole group the urine output was about equal during the day and night. In people with no nocturnal voiding episodes, but with one episode at 08.00 hours the urine output during the day was 1.8 times higher than at night. The more voids during the night the greater was the proportion of the diuresis occurring between 20.00 and 08.00 hours. In people with 1, 2 or ≥3 nocturnal voids the ratios between the diurnal and nocturnal urinary output were 1.1, 0.9 and 0.8, respectively (Fig. 3) [29,30].

In a study of the relation between urine output and voiding frequency, there was a greater inter-individual difference in the pattern of both these variables in women than in men (Fig. 4) [29]. Furthermore, in none of the investigated subjects was a larger urine output in the daytime associated with more voids in the night [29]. The bladder can contain a third more urine at night than in the daytime (Fig. 5) [29]. This means that if an elderly person tells a physician that he or she urinates more often between 20.00 and 08.00 hours than between 08.00 and 20.00 hours it is highly probable that nocturnal urinary output is increased [29].

It can be concluded from the results of the latter study that in the presence of a normal bladder capacity the main explanation for the occurrence of frequent nocturnal voids, with no corresponding increase in voiding in the daytime, is nocturnal polyuria due to a disturbance in the AVP system [12,33,34].

Nocturnal polyuria

The nocturnal fraction of the 24-h urine output (23.00–07.00 hours) increases with increasing age [26,31]. Among healthy men and women aged 21–35 years, this nocturnal fraction was ≈14%, whereas the corresponding fraction in elderly men and women was 34% [31]. Nocturnal polyuria has been defined as a nocturnal fraction of >20% of the 24-h urine output in young adults and 33% in elderly individuals [15,35,36].

Nocturnal polyuria syndrome (NPS)

In men and women the circulating AVP levels increase with increasing age. This may be a compensatory mechanism, as there is a concomitant decrease in the sensitivity of AVP receptors in the kidney [37,38]. In some cases there is a deterioration of the 24-h rhythm of AVP and the plasma concentrations of the
hormone are decreased to very low or even undetectable levels [Fig. 6] [12,29,33]. A disorder of the AVP system with such very low or undetectable levels of AVP at night and in some cases throughout the whole 24-h period has been designated NPS. This condition is characterized by an increase in the nocturnal urine output, in the most extreme cases reaching 85% of the 24-h diuresis [29,39]. The occurrence of NPS in an elderly population aged ≥65 years has been estimated to be 3–4%. In many cases the lowest AVP levels are at night, in contrast to the conditions in elderly people in general. In some elderly individuals, the AVP level in the plasma is not detectable at any time of the day or night [33].

There is a close correlation between nocturia and nocturnal polyuria in the elderly (Fig. 4) [29]. In NPS the 24-h diuresis is normal or moderately increased [40]. The condition is also characterized by increased thirst, which is most pronounced at night [1].

Not only the nocturnal diuresis but also diurnal diuresis is increased in elderly people with an impairment of the AVP system. In a study of 17 men and six women (mean age 68.1, SD 4.7 years) with nocturia (defined as two or more nocturnal voids) and a nocturnal urinary output of ≥0.9 mL/min, plasma AVP was assayed at noon and midnight, and urine collected [40]. In the whole group the mean (so) diurnal urine output was 1358 (664) mL, the nocturnal urine output 796 (312) mL and the total 24-h urine output 2154 (712) mL. The nocturnal diuresis rate was higher than the diurnal rate in two-thirds of study subjects. The 24-h diuresis was 2848 (732) mL/24 h in persons with no detectable AVP at midnight and 1910 (534) mL/24 h in those with detectable AVP (P < 0.01). The rates of diuresis in these two groups were 2.0 (0.5) and 1.3 (0.4) mL/min, respectively (P < 0.01). The diurnal urine output was 2081 (835) mL in people with no detectable AVP at midnight and 1103 (350) mL in those with detectable AVP at that time (P < 0.001) [40].

Higher nocturnal urine volumes in nocturics than in non-nocturics was also recently reported by Rembratt et al. [38]. Furthermore, they found that there was also an increase in the diurnal urine voided volume in men with nocturia, but a decrease in women. The mean voided volume was 85 mL less in nocturic than in non-nocturic people [38].

**LOSS OF BLADDER CAPACITY**

Diminished voided volumes may also be a factor related to an increased nocturnal urinary frequency [36]. Among the conditions that may contribute to such bladder storage problems are urogenital ageing, bladder hypersensitivity, BOO and detrusor overactivity (overactive bladder) [15,41].

In a study of the prevalence of a low nocturnal bladder capacity, perhaps more accurately, ‘reduced voided volumes’, in the elderly, Kawauchi et al. [42] analysed the nocturnal urinary frequency, time of voiding and amount of each void in 188 healthy men (mean age 67.1 years) with no prostatic disease. The nocturnal urinary frequency increased with age from a mean of 0.61 voids per night at 55–59 years to 1.2 at 75–79 years [42]. However, multiple regression analysis showed that nocturnal voided volumes and nocturnal urinary volume were independent determinants of nocturnal frequency; age was not an independent factor [42].

**NOCTURIA IN RELATION TO MEDICATION**

Diuretic drugs are associated with a doubling in nocturia in both men and women [16]; this may be partly because most patients take these oral medications in the morning. In a study by Reynard et al. [43] diuretics taken 6 h before going to bed resulted in substantially less nocturia. In contrast to these results, a recent study Rembratt et al. [44] found no significant correlation between nocturia and diuretic use, when diuretics were presumably used for heart failure/hypertension.

The occurrence of ≥3 nocturnal voids was reportedly three times higher in women using analgesics daily than in those not using analgesics [18]. This finding could be a proxy for the aches and muscle cramps associated with nocturia [1].

**MANAGING NOCTURIA**

**LIFESTYLE FACTORS**

Managing nocturia is best based on an approach that targets the underlying causes, but changes in several empirical lifestyle factors might be effective. Restriction of caffeine and alcohol intake may help some patients with nocturia [15]. Fluid restriction before bedtime may help to alleviate the disorder, especially in patients who also have urgency incontinence [45,46]. Griffiths et al. [46] studied 128 incontinent elderly patients and found that evening fluid restriction reduced nocturnal urine excretion by a small amount in those with severe urgency incontinence. Some data suggest that this method alone may not be ideal for alleviating nocturia in the elderly. For instance, Asplund and Åberg [1] found that nearly half of those who woke ≥3 times a night to urinate already restricted their fluid intake in the evening.
cases of nocturnal polyuria, the urine output cannot be reduced by restricting fluid intake, because of a lack of circulating AVP and an inability to respond with inhibition of the diuresis after fluid restriction. Such patients therefore need to drink at night.

Patients whose nocturia is thought to be related to diuretic use can be counselled to time their dosage so that diuresis is complete at bedtime. As noted, Reynard et al. suggested that diuretics should probably be taken 6–8 h before retiring. They found that frusemide given 6 h before bedtime substantially reduced nocturia in men with LUTS whose most pronounced symptom was nocturia [43].

**PHARMACOLOGICAL THERAPY**

Desmopressin is a synthetic analogue of AVP that, theoretically, should help to control both nocturnal diuresis and nocturnal voiding. The postulated efficacy of desmopressin was supported by the results of a series of trials conducted among healthy, community-dwelling Swedish men and women aged 60–74 years who had nocturia (≥2 nocturnal voids) and nocturnal polyuria (≥0.9 mL/min) [47,48]. An open dose-titration trial of desmopressin including 23 subjects from this same population showed that higher pretreatment nocturnal diuresis (≥1.3 mL/min) was associated with a greater reduction in nocturnal urinary volume. Patients with a baseline nocturnal diuresis of <1.3 mL/min were less likely to respond (Fig. 7) [47]. Patients were given desmopressin 100, 200 or 400 μg/day for 2 weeks. A dose of 200 μg was slightly more effective in all patients than 100 μg, and 400 μg did not further decrease the urinary output. Nocturnal diuresis returned to the pretreatment level immediately after discontinuing desmopressin therapy [47].

Subsequently, a randomized, double-blind, crossover trial of efficacy (17 patients, mean age 67.7 years) was conducted in which patients received 2 weeks of titrated daily desmopressin therapy or placebo. The desmopressin group had significantly less mean nocturnal diuresis than the placebo group (1.0 vs 1.6 mL/min; \( P < 0.001 \)). The desmopressin group also had significantly fewer nocturnal voids than the placebo group (1.1 vs 1.7; \( P < 0.001 \)) and a mean time to first awakening that was 1.4 h longer. The diuresis over 24 h varied only minimally [49].

Rembratt et al. [50] obtained similarly promising results in a 3-day study of desmopressin safety, comprising 72 Swedish community dwellers (mean age 75.5 years) who reported having ≥2 nocturnal voids. The number of episodes of nocturnal voids decreased by a mean of 1, and 82% of the patients showed a ≥20% reduction in nocturnal diuresis. The time to first nocturnal void increased by a mean of 1.9 h [50].

Although theoretically desmopressin may allow dilutional hyponatraemia to develop when the fluid intake exceeds physiological needs [50], no participant in either the 1998 or 1999 study by Asplund et al. [47,49] had significant changes in water or sodium balance, perhaps because the agent was active only at night rather than over 24 h. However, Rembratt et al. [50] proposed that the risk of hyponatraemia during desmopressin therapy should be actively addressed. They recommended screening for low serum sodium levels both before starting treatment with an AVP analogue and after a few days of therapy. In their previously cited study, 8% of patients (six of 72) were sodium-sensitive (defined as a mean serum sodium level deviating by >5 units from baseline during desmopressin therapy) [50]. Sodium sensitivity appeared more likely in patients with concomitant heart disease (OR 10.0, 95% CI 0.9–105.8), increasing age (1.3, 1.1–1.6) and high baseline 24-h urine output (1.2, 1.0–1.5) [50].

Patients with nocturia associated with detrusor overactivity, a component of overactive bladder syndrome and the common symptom of urgency incontinence [41], may respond to drugs that affect bladder contractility. These drugs include the antimuscarinic agents oxybutynin, tolterodine and solifenacin, which can substantially reduce the voiding frequency in patients with overactive bladder [48,51–53]. Solifenacin and other new antimuscarinic drugs in development for treating overactive bladder, e.g. darifenacin, have potentially better safety and tolerability profiles than the older antimuscarinic agents [53–55].

**CONCLUSION**

Nocturia is relatively common among the elderly and becomes increasingly prevalent with age, with profound influences on health and quality of life. Not only is it associated

![FIG. 7. Change in nocturnal diuresis during treatment with desmopressin in different doses given at bedtime in relation to the initial nocturnal diuresis. Adapted with permission from Asplund et al. [47].](image)
with poor sleep, increased nightmares, night-time symptoms such as giddiness, leg tingling and muscle cramps, daytime fatigue, poor balance, a greater risk of falls, and self-reported poor health status, but it also appears to predict a higher risk of death. Factors that may be implicated in nocturia include age-related changes in the circadian rhythm of diuresis as a consequence of deterioration of the AVP system, nocturnal bladder capacity, and certain diseases and medications. In some cases, nocturia can be alleviated by lifestyle changes such as fluid restriction and careful timing of diuretic dosages, although these modifications do not appear to be consistently effective. In addition, some pharmacological therapies are effective, notably desmopressin, an analogue of AVP, and antimuscarinic agents.

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Abbreviations: OR, odds ratio; AVP, vasopressin; NPS, nocturnal polyuria syndrome.
A developing view of the origins of urgency: the importance of animal models

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Although caution should be used when applying animal data to human physiology, if care is taken to differentiate between general principles and complications of detail, particular to the species being examined, then experimentation on animal models can reveal basic phenomena in the bladder that offer clues to the origin of urgency. Recent data from the whole isolated bladder of guinea pigs showed unexpected complexities in autonomous activity during the filling phase of the micturition cycle: small, transient increases in intravesical pressure were associated with propagating waves of contractile activity and localized stretches of bladder wall. This complex, coordinated activity suggests that there are mechanisms within the bladder wall devoted specifically to generating phasic activity. Thus, there appear to be two systems controlling detrusor contractions: one associated with overall contractions similar to the micturition contraction and the other generating phasic activity. The mechanisms generating the phasic activity appear to be the point of complex integration of both excitatory and inhibitory inputs. There is evidence that local activity in the bladder wall generates afferent discharge, which probably contributes to bladder sensations. Animal data suggest a novel motor/sensory system incorporating contractile (motor) events, which cause stretches resulting in activation of afferent nerves (sensory). The motor element of this system appears to be controlled in a highly complex fashion such that the amplitude and frequency of the motor activity can be modulated by a variety of inputs. This raises the possibility that the sensitivity of the system informing the central nervous system, and thus awareness of the bladder’s state during the micturition cycle, can be manipulated, possibly via novel drugs targeted at areas involved in overactive bladder, including urgency incontinence.

KEYWORDS
urgency, bladder, filling phase, phasic activity, nonmicturition contractions, autonomous activity, micromotions

INTRODUCTION

In this short review I take a sideways look at the current views of bladder function and the origins of bladder sensations. Failure to take into account basic observations made many years ago has constrained the thinking about the mechanisms that generate sensations in the bladder. When these observations are reconsidered and extended, a new perspective on the physiology of the bladder emerges, particularly for the filling phase of the micturition cycle. The systems being discovered open new avenues for investigating the origins and physiological control of sensation in the bladder. Importantly, increasing knowledge of the physiology of the bladder has the potential to lead to a more fundamental understanding of the origins of clinical disorders such as urgency and urgency incontinence.

HISTORICAL OVERVIEW OF THE VALUE OF ANIMAL STUDIES

Control of the urinary bladder is of considerable clinical importance and has been the focus of a great deal of attention from both clinicians and basic scientists. Over the past century, experimental work on human bladder function has focused primarily on cystometric in vivo investigations and cellular, molecular and morphological studies of biopsy material. Because experiments in humans and human material raise legal, moral and ethical dilemmas, such studies are inherently limited. For example, it is not possible to study experimentally the cellular processes in the CNS that control micturition in humans. It also is becoming extremely difficult to acquire significant amounts of bladder tissue from healthy normal subjects for investigating cellular physiological events. Thus, basic science has resorted to using tissue from animal models to gain insights into the principles governing integrated control of the lower urinary tract and its cellular components.

It may not be unreasonable to suggest that the general principles regulating bladder function in mammals should be similar among different species. It also is not unreasonable to suspect that the detailed morphology, and the cellular and molecular mechanisms involved, may be different. Thus, caution should be exercised when applying animal data to human physiology. It is crucial to identify which are general principles and which are ‘complications’ of detail. This difficulty was recognized at the beginning of the last century in some of the earliest studies of bladder physiology. In an investigation into the actions of nerves on the bladder, Elliot wrote in 1905:

To determine the nervous control of the bladder with its simple structure and single function might seem not hard task. Yet some of the main facts are still disputed. The experiments of this paper reconcile most of these differing observations by showing that the innervation of the bladder varies from animal to animal, and that the error [conflicting data from different investigators] was the old one of arguing from the particular to the universal [1].

Over the next 60 years, this difficulty of ‘arguing from the particular to the universal’ had an important influence on the development of the understanding of the bladder and its functions. Among those interested in clinical urology, it was strongly argued that animal studies were of little relevance. Consequently, urologists focused on human studies, despite their limitations, apparently being minimally influenced by...
principles unravelled in other species. In 1960 in the Handbook of Physiology, Ruch wrote:

Although neurologists, urologists and physiologists have a community of interest in the bladder, they have little community of thought. The clinical disciplines have developed a fairly uniform view, apparently little influenced by physiological experiments on animals although there is a substantial similarity in methodology which should make translation from animals to man easy [2].

It is arguable whether this situation has changed throughout the years. In clinical research, the 'fairly uniform view' has been expanded and refined but remains relatively basic. At its very simplest, this view accepts that that are two phases of the micturition cycle, i.e. filling and voiding. The bladder is a quiescent, compliant reservoir during filling, and the onset of voiding is determined by the CNS. The initiation of micturition involves a complex reflex in which afferent input from stretch receptors in the bladder wall is integrated with other inputs in the pontine micturition centre and, when appropriate, this region of the CNS controls and coordinates sphincter relaxation, detrusor contraction and urine expulsion. The micturition contraction is triggered by postganglionic parasympathetic nerves with acetylcholine acting on muscarinic M3 receptors on the bladder smooth muscle to raise intracellular Ca++ [3].

The clinical perspective has developed to the point where the urinary system is conceived of as a 'black box' regulated according to the fairly uniform view of how the system functions.

In recent decades, one of the major forces driving lower urinary tract research has been the goal of discovering the origins of detrusor overactivity, urgency and urgency incontinence, and effective means to treat these conditions. The 'black box' technique has been widely adopted. In short, the approach has been to take a variety of basic drugs and their pharmaceutically designed derivatives, prescribe them to patients, and then attempt to determine their efficacy by assessing positive or negative outcomes. This method does not facilitate understanding of the fundamental mechanisms involved. One consequence has been that new insights into the physiological factors controlling the human bladder have been slow to emerge.

It is becoming clear that this simplistic approach will not suffice. Accumulating data suggest that the mechanisms involved in controlling bladder function are much more complex than supposed, and that these complexities must be discovered and taken into account. One example of this is the development of antimuscarinic drugs to treat overactivity and urgency incontinence. The clinical rationale for using these agents has been that they interfere with the detrusor contractions that are associated with the sensations of urgency [4]. For this reason, antimuscarinic drugs have been developed, intensively investigated clinically, and widely advocated for the treatment of the overactive bladder. Drugs such as tolterodine and oxybutynin, as well as the new agents darifenacin and solifenacin, reduce detrusor contractility and alleviate the symptom of urgency. At first glance, this is a positive outcome and a clinical advance. There can be no doubt that these drugs benefit patients suffering from detrusor overactivity, causing urgency and urgency incontinence. However, a scientific difficulty is posed, in that at clinically effective doses that reduce urgency, these agents do not significantly affect micturition contractions [4]. Such data imply that the neuromuscular junction is not the active site for these drugs at therapeutic doses [4,5]. This is not what was predicted from the 'fairly uniform view' and implies that there has to be something else in the 'black box. Other examples of an oversimplified fairly uniform view include the lack of clear physiological roles for: (i) purinergic, adrenergic, nitric and peptidergic nerves (substance P, vasoactive intestinal peptide and calcitonin gene-related peptide, CGRP); (ii) the intramural and pelvic ganglia; (iii) the urothelium; and (iv) specialized cell types such as interstitial cells. For a full picture of the physiology of the bladder and its control mechanisms, all of these component systems should be considered. In this respect, animal-model experiments on the integrated control of lower urinary tract function can be extremely powerful. Further, such research is the only way to derive general principles that will affect the understanding of the human system. The following sections describe a single, highly specific view of how a comprehensive approach to bladder function may reveal complexities and interconnections between apparently unconnected observations and mechanisms. The data show that basic phenomena in the bladder remain unknown; revealing these mechanisms will advance our fundamental appreciation of these processes.

THE PHYSIOLOGY OF THE FILLING PHASE

In normal subjects, bladder sensations increase as the bladder fills. In patients with overactive bladder and urgency, these sensations can be excessive and lead to urgency incontinence. The activity of the bladder during the filling phase is central to the origins of sensation. Therefore, it seems obvious that the physiology of the filling phase should be examined to understand the causes of urgency and urgency incontinence.

It is widely thought that the human bladder is not active during the filling phase [6]. Furthermore, it has become generally accepted that any detrusor activity during filling is pathological [6]; however, this is not actually true. There is a body of evidence indicating that the bladders of healthy young subjects are capable of generating phasic increases in pressure during the filling phase (see [7–9] for an overview). The original observations of Mosso and Pellacani [10] on nonrhythmic contractions in the human bladder before voiding made more than 120 years ago; however, they seem to have been forgotten. In animals, the situation is clearer. It has been known for over a century that the bladder is active during filling: again, the original observations of this phenomenon in cats were made in 1892 by Sherrington [11]. Indeed, Sherrington also showed that this phasic activity originated in the absence of any CNS input and occurred when the bladder was removed and maintained in vitro. A plausible conclusion is that this is an autonomous activity, which should be an inherent property of the bladder wall. However, since 1892 there have been few detailed studies of nonmicturition or autonomous activity; the absence of basic information about these processes represents a fundamental gap in the understanding of the physiology of the lower urinary tract [7,8].

The forgotten aspects of spontaneous activity in the whole bladder prompted a reevaluation of its manifestations, the mechanisms involved, and the possible physiological roles it may play. In a series of recent papers, the nature of autonomous activity was described using the isolated whole bladder of the guinea pig [9,12]. These experiments revealed unexpected
complexities in the nature of the spontaneous activity: small transient increases in intravesical pressure were associated with propagating waves of contractile activity and localized stretches of the wall. This complex coordinated activity suggested the presence of mechanisms within the wall devoted specifically to generating phasic activity. Subsequent experiments showed that the ‘autonomous activity’ was augmented by muscarinic agonists and nicotinic ligands [9,12]. This ‘augmented activity’ consists of phasic increases in intravesical pressure of 10–20 cmH\textsubscript{2}O [12]; each transient increase is associated with waves of contractile activity and discrete stretches of the bladder wall. These observations led to the conclusion that there are two systems within the bladder generating contractions: one associated with the overall contractions of the detrusor similar to the micturition contraction and the other generating complex phasic activity [12] (Fig. 1) [13–15].

Support for the presence of two systems controlling bladder contractions emerged from studies conducted to determine the actions of an analogue of ATP, i.e. α,β methylene ATP (α,βMATP) and substance P on the isolated whole bladder [13]. The data showed that α,βMATP and substance P at low doses (<300 nmol/L) had little direct effect on the resting whole bladder in terms of producing overall contractions. In contrast, the same or lower doses dramatically increased the frequency of the phasic contractions (Fig. 2). These observations, in addition to showing that there may be two distinct systems involved in effecting detrusor contractions, also suggest important regulatory roles for ATP and substance P in the bladder wall [13]. The sources of these agents are not known, but nerve fibres containing ATP and substance P are found throughout the bladder wall. In addition, ATP (and nitric oxide, NO) are released from the urothelium [16–18]. These different physiological inputs appear to act on the phasic mechanism.

An enigma of bladder physiology has been the role of adrenergic, peptidergic and nitrergic nerves. In some species, adrenergic nerves reduce bladder tone and the micturition contraction, whereas in others there is no effect. Furthermore, although the bladder has many nerves containing CGRP, no specific function has been ascribed to them. Examination of the effects of noradrenaline and CGRP on the phasic activity in the isolated bladder showed that these agents inhibit phasic activity (Fig. 3; [14], Gillespie, unpublished observations). Taken together, these observations suggest that the mechanisms generating phasic activity involve complex integration of both excitatory and inhibitory inputs.

**FIG. 1.** Complex contractile activity generated in an isolated whole bladder preparation (guinea pig). (a) shows records of intravesical pressure during repeated brief exposures to varying concentrations of carbachol. (b) and (c) illustrate on expanded time bases the records at 0.3 and 10 μmol/L, respectively. At the lower dose, the phasic activity predominated, whereas at the higher dose the phasic activity is superimposed on a slower contracture. Reprinted with permission from Gillespie et al. [12]. (d) illustrates an overview of the mechanisms involved in these complex responses: (1) represents the ‘classic’ view of detrusor activation involving parasympathetic cholinergic neurones; (2) illustrates distinct mechanisms generating phasic activity. Excitatory and inhibitory inputs from the CNS and the urothelium may affect the frequency and amplitude of the activity [13], and intracellular mechanisms involving cAMP and cGMP also have a role [14,15].

**LOCAL REFLEXES IN THE BLADDER WALL**

Autonomous activity in the isolated bladder increases as the bladder is filled [9]. Figure 4 shows that phasic activity, augmented in the presence of a muscarinic agonist, also increases as the bladder volume rises. This observation is deceptively simple. It raises...
basic questions about the nature of the mechanism that senses bladder volume and how the output from these elements becomes integrated to influence phasic activity. These questions remain unanswered, but they suggest the possibility of 'local reflex' mechanisms operating in the bladder wall that may be involved in some way in modulating detrusor activity.

The components of such a reflex are unknown. One possibility involves sensory nerves. Sensory nerve endings lie in the suburothelial spaces [19], and in many tissues these axons produce collaterals that remain in the tissue. Such a microanatomical arrangement was first described by Bayliss [20] in 1901 to account for local vasodilator reflexes in the skin. Activation of the afferent fibres results in antidromic activation of the collaterals, which then have their effect on the tissue. This local axonal reflex has been suspected in many other tissues, including the bladder (see Maggi and Meli for a review [21,22]). In an attempt to discover evidence of any involvement of afferent nerves in the volume-induced responses, bladders were treated with capsaicin to effectively eliminate Aδ- and C-fibre responses. One of the actions of capsaicin is to initially stimulate nerves, causing them to release the contents of their terminals [21,22]. Applying capsaicin to whole isolated bladders caused transient complex changes in the frequency of the phasic activity: an initial increase, a decrease and a secondary increase (Fig. 5). This may be the consequence of a capsaicin-induced release of substance P and CGRP, with consequent excitatory and inhibitory effects (see above) [13,21,22]. A tentative conclusion is that sensory nerve activity may affect phasic activity, which may implicate local antidromic reflexes involving axon collaterals.

The volume-induced changes were not affected by capsaicin treatment, nor were they affected by tetrodotoxin (Gillespie, unpublished observations), suggesting that although these axonal reflexes may modulate phasic activity, nerves using Na+ channels or Aδ- or C-afferent nerves are not involved with the primary mechanism generating volume-induced activity. Thus, other components should be considered. It was suggested recently that interstitial cells in the suburothelial space may serve some form of sensory function [23–25]. It is not known how these cells contribute to sensation and how this mechanism may operate physiologically,
but they could play a role in volume responses.

The above section shows that there are basic phenomena relating to the integrated physiology of the bladder that have yet to be described. The physiological role of these complex systems is not known, but it is worth speculating whether they can be integrated into a coherent picture of complex bladder functions that are not associated with micturition.

MICROMOTIONS AND SENSATIONS

A potentially important clue to the role of this complex activity can be traced to the observations of Coolsaet and others [26,27] of small localized contractions, which they described as 'micromotions', in the bladder wall of the pig. However, the mechanisms generating these events were not investigated, nor was their physiological role considered in any detail. It was speculated from these observations that each micromotion, as it was localized, could lead to a 'microstretch'. These localized stretches could, in turn, excite afferent nerves and contribute to bladder sensations [26]. The phasic activity of the guinea pig bladder (described earlier) confirms and extends this idea. In the guinea pig the contractions can be large, allowing stretches of the wall to be clearly demonstrated. Thus, an important concept is that localized activity generating local stretches may activate afferent discharge.

Published evidence suggests that this is a credible idea. The original work by Iggo [28] to investigate afferent nerve discharge from the cat bladder showed that there was a population of adapting stretch receptors in the bladder wall. These receptors fell silent in the presence of a constant or slowly changing stimulus, but were clearly active during rapid filling or during the rising phase of spontaneous phasic contractions that occur in the cat bladder (Fig. 6) [11]. These observations were confirmed by showing that there is a definite correlation between bursts of afferent discharge in the pelvic nerve of the cat and phasic pressure changes [8]. Thus, there is evidence to suggest that local activity in the bladder wall can generate afferent discharge. The afferent discharge more than likely contributes to bladder sensations.

It can be concluded that what may be present is a 'motor/sensory' system incorporating contractile (motor) events, which cause stretches resulting in activation of afferent nerves (sensory) (Fig. 7). The data summarized here suggest that the motor element of this system may be controlled in a highly complex fashion such that the amplitude and frequency of the motor activity can be modulated by a variety of inputs. The key input may be that derived from the volume of fluid in the bladder. By this mechanism, bursts of afferent discharge proportional to bladder volume may be relayed to the CNS. Other inputs to this motor/sensory system, involving certain neurotransmitters (substance P, CGRP, noradrenaline, NO), may indicate the involvement of extramural nerves, whereas others involving ATP and NO may suggest components derived from the urothelium. The overall emerging concept is of a modulated sensory system.

**FIG. 4.** The effects of increasing intravesical volume on muscarinic-induced phasic activity in the isolated whole guinea pig bladder. (a) upper panel, shows an original record from an experiment where the intravesical volume was increased from an initial value of 700 μL in increments of 200 μL to a final volume of 1700 μL. The lower panel shows an analysis of this record in which the instantaneous frequency (reciprocal of inter-spike interval) is plotted against time. (b) shows sections of the record on an expanded scale (Gillespie, unpublished observations).

**FIG. 5.** The effects of capsaicin on muscarinic-induced phasic activity. The upper panel shows data from one experiment where a bladder was exposed to capsaicin (30 μmol/L). On applying capsaicin there was a complex series of changes involving an initial increase, a decrease, and a secondary increase. The lower panel shows the data analysed in terms of changes in instantaneous frequency (Gillespie, unpublished data).
It is important to realise that the integrated actions of such a system have not yet been confirmed unequivocally. However, if such a system does exist, then it has the potential to relay information to the CNS about bladder volume; inputs from the bladder wall and the CNS could potentially modulate related sensations. By involving such a complex series of interrelated mechanisms, it would be possible to increase and decrease the sensitivity of the system informing the CNS and therefore consciousness about the state of the bladder throughout the micturition cycle.

RELEVANCE TO HUMANS

The data presented above indicate that complex mechanisms serving basic physiological processes are present. However, it is clear that little is known about the detailed integrated physiology of the bladder wall and the structures involved. In the case of autonomous activity, data are highly suggestive that this system plays a role in generating and modulating sensations originating in the bladder wall. The system is complex, perhaps because it is involved in both these functions. It has only been possible to gain a perspective on this sensory system from a detailed analysis of the whole isolated organ. Such complex events could not have been predicted from data on small isolated pieces of muscle or single cells, or from molecular data. Moreover, these experiments are typically not feasible using the human bladder. This, once again, shows the importance of animal models for revealing basic principles of bladder function and control.

The possibility of a potential novel motor/sensory mechanism in animal bladders elicits the query: "does this motor/sensory system operate in humans?" This question cannot be answered at present. However, if nonmicturition phasic activity and its modulation are general principles, then they will become apparent in future studies on the human bladder. There is circumstantial evidence for such activity from ambulatory monitoring studies in normal human subjects [29,30] and in women with chronic pelvic pain [31]. Although it is unlikely that exactly the same phenomena are present in the human bladder, it is probable that there is some form of motor/sensory system. The challenge for the coming years will be to identify such a
system in humans and to elucidate its underlying mechanisms. One research focus will be to determine if this system is involved in the aetiology of detrusor overactivity and associated symptoms such as sensory urgency. Due to its number of inputs and varied pharmacology, this motor/sensory system may be a productive hunting ground for the design of new drugs aimed at specific targets affecting overactivity and urgency incontinence. Such research may provide insight into the actual therapeutic mode of actions of currently used drugs such as the antimuscarinics. However, a word of caution should be reiterated: any new insight into how an animal system may function only relates, in the first instance, to that species. It is hoped that further experimentation will yield new general principles. The important advances will come from recognition of what is particular and what is universal.

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Abbreviations: CGRP, calcitonin gene-related peptide; αββMATP, αβ methylene ATP; NO, nitric oxide.
Introduction

Urgency is a major component of the overactive bladder syndrome (OAB), but there is no standardized, objective method for assessing this important subjective complaint [1], nor is there a satisfactory means to demarcate urgency, which leads to incontinence, from the sensations that came before it. In addition, there is little agreement about how best to incorporate a uniform definition of urgency and OAB into clinical practice [2]. This has important implications for evaluating patient response during a urodynamic study and assessing the benefits of therapy.

The ideal descriptors of urgency and its progression should have objectively delineated, easily comprehensible meanings (in any language) that enable patients to classify the perceived range of urge sensations without prompting or discussion by the investigator. The Standardisation Sub-committee of the ICS currently recognises ‘urgency’ as a ‘sudden and compelling desire to pass urine, which is difficult to defer’ [3]. The term is imprecisely defined in this fashion, because it implies different levels of severity to individual patients.

A more recently proposed international standard, the International Urgency Severity Score, is a psychometrically validated, four-level scoring approach that assesses the degree to which sensations of urgency interfere with the ability to continue with activities or tasks [4]. A potential limitation of the International Urgency Severity Score is that it was validated in a population of patients with OAB in whom the predominant complaint was urgency incontinence, rather than urgency. Furthermore, ‘urgency’ itself was not specifically defined.

Bladder Sensations and Urgency

The objective cystometric evaluation of urgency and urgency incontinence is focused on identifying involuntary detrusor contractions. These contractions tend to correlate with symptoms of urgency and urgency incontinence [5], but the clinical significance is often unclear [1,2,6–8]. Patients with extreme symptoms of urgency may have completely normal cystometrograms [1], whereas a large proportion of otherwise healthy, asymptomatic individuals may have obviously abnormal detrusor activity at baseline [9].

Recently, Oliver et al. [1] explored whether the lower tract sensation of urge can be categorized by patients in a useful and reproducible fashion for implementation as an evaluation measure in OAB, and whether urgency may be improved with neuromodulation therapy. It is not clear whether or not urgency can be graded; there seems to be a lesser state of urgency in which the desire to void is frequently, but not invariably, deferred via appropriate strategies. Sensation (urgency) increases, and severe urge represents a stage immediately preceding the advent of true urgency. The sensation of urgency may occur at low bladder volumes, and for some patients with urgency, the antecedent sensations of needing to void, and bladder fullness, may be the most distressing of their LUTS.

There is evidence to suggest that sensations of bladder fullness are experienced by...
patients in a reproducible fashion during filling cystometrography (CMG), and that these sensations are important variables in assessing voiding patterns [10,11]. Wyndaele [11] studied the normal perception of bladder filling and desire to void during filling CMG. In that study 38 healthy subjects (28 men and 10 women, aged 19–28 years) were cystometrically evaluated; four men in the study presented with detrusor overactivity. The results showed a reproducible three-step sequence of subjective sensations during normal bladder filling in the 34 subjects with no detrusor overactivity: (i) first sensation of bladder filling (FSF); (ii) first desire to void (FDV); and (iii) strong desire to void (SDV). These three levels of sensation were easily distinguishable, consistent across all 34 subjects, and highly correlated with underlying bladder volume in each individual, and were reported without prompting by the investigator [11].

In standard practice the three levels of subjective sensations in patients are normally recorded on the cystometrogram after prompting (Fig. 1). A fourth level that has been described as ‘an urgent desire to void’ is sometimes used, where a patient cannot ‘hold on’ and delay voiding any further. Clearly, if prompting can be avoided, then patients would be less likely to give biased or misleading responses; for this purpose a more objective approach to recording the sensations would be desirable.

**NEUROMODULATION OF BLADDER SENSATIONS**

Neuromodulation of involuntary detrusor activity by sacral nerve stimulation or stimulation of pudendal afferent fibres improves LUTS and has become a standard of care for treating refractory OAB [12–17]. The suppression of involuntary detrusor contraction by electrical means is associated with improvement in urgency, which then presumably leads to concurrent inhibition of bladder sensations [1]. However, implantable sacral nerve stimulators are not effective in all patients. Urodynamics alone has been a poor predictor of successful outcome; in one study, neuromodulation was unsuccessful in more than a third of patients chosen after cystometry [18]. Sensation scores may be potentially more pertinent to patient selection for implanting a permanent sacral device.

To assess the effects of electrical neuromodulation on bladder symptoms, including urgency, it was first necessary to establish a clear, objective means for describing the full range of lower urinary tract sensations perceived by the patient [1]. After establishing that bladder sensations provide a meaningful alternative to the traditional focus on detrusor overactivity in the evaluation of OAB, it was subsequently shown for the first time that bladder sensations could be profoundly suppressed by neuromodulation, and that these favourable changes in sensation occurred concurrently with substantial underlying improvements in bladder capacity.

**AN OBJECTIVE MEASURE OF SENSATION**

It has been shown that patients with urgency incontinence similarly describe an increasing sense of urgency with bladder filling that can be measured reliably and reproducibly using a patient-activated device [19]. This technique involves a small keypad (the ‘urge keypad’) that is operated solely at the discretion of the patient, with no interference or influence from the investigator. The ‘urge keypad’ manipulates a five-level, push-button and light-emitting-diode scoring system, representing increasing levels of bladder awareness and an intensifying need to void.

**FIG. 1. Normal sequence of recorded subjective sensations during cystometrography.** In standard practice the three levels of subjective sensations in patients are recorded on the cystometrogram after prompting. A fourth level which might be described as urgency is sometimes used where a patient cannot ‘hold on’ and delay voiding any further. Pves, vesical pressure (total bladder pressure); Pabd, abdominal pressure measured rectally; Pdet, detrusor pressure, where Pdet = Pves – Pabd. This subtraction is normally tested throughout filling by asking patients to cough (C).
The ‘urge keypad’. Operating independently of investigator prompting, subjects press buttons indicating five levels on the scale, 0 (none), 1 (slight; FSF), 2 (moderate; FDV), 3 (strong; SDV) and 4 (desperate), as their subjective sensations change during bladder filling. Only one button can be pressed at a time. An electrical output from the keypad for each level of sensation can be recorded alongside the other cystometrogram traces shown in Fig. 1. Scores from this subject-driven device offer a reliable, reproducible profile of sensations experienced during bladder filling. Abbreviations as for Fig. 1. Adapted with permission from Oliver et al. [1].

Validating the ‘urge keypad’. Sensation scores entered on the ‘urge keypad’ during filling cystometry by a patient with urgency incontinence. Fluid was both added and removed. The typical ‘staircase’ tracing of scores shows increases in score with infusion and decreases with fluid removal. Detrusor activity appears to occur directly before score increases. Pdet, detrusor pressure. Adapted with permission from Oliver et al. [1].

EFFECTS OF NEUROMODULATION ON THE MEASURED SENSATIONS OF URGENCY

In Oliver et al. [1], 35 patients (19 men and 16 women) were studied prospectively; all patients underwent CMG at study entry and during neuromodulation. Electrical stimulation was applied to pudendal afferents via the dorsal penile nerve or dorsal clitoral
nerve at maximum tolerable strength. Patients reported urgency episodes spontaneously using the "urge keypad".

Of the 35 patients studied, 31 (89%) had suppression of bladder sensations including urgency, and improved bladder capacity. A representative tracing from one patient is shown in Fig. 6. In the group of responders, neuromodulation increased the mean bladder capacity at every sensation level compared with baseline CMG, although the effect was most pronounced for the lowest levels (i.e. mild and moderate). Responding patients had a clearly greater delay until the appearance of first bladder sensations, followed by characteristic staircase-like increases, heralding the advent of higher levels of sensation and culminating in a strong or desperate desire to void at a significantly higher volume. Greater degrees of bladder sensation were consistently suppressed with neuromodulation in most patients, although to a somewhat lesser extent and with a smaller change in bladder capacity. Overall, the magnitude of increased bladder capacity achieved was statistically significant in 20 (57%) of the patients. The mean (SD) increase was 94.8 (48) mL (Table 2) [1]. The increase in bladder capacity with neuromodulation was equivalent in some patients to that which would be expected after treatment with antimuscarinic medication; this was consistently so among those who had spinal cord pathology. Nine patients underwent baseline control CMG three times before filling under neuromodulation. In these patients, the percentage increase in bladder capacity for any given sensation score was significantly greater than that potentially attributable to changes in bladder wall compliance due to repeated bladder filling (Fig. 7).

Similar results have been obtained with sacral nerve stimulation, specifically during peripheral nerve evaluation testing in four patients who were potential subjects for implantation of a pulse generator and stimulating electrode at the S3 level [10]. Peripheral nerve evaluation testing is the customary method to determine whether a patient is a candidate for implantation (e.g. a sacral foramen stimulator implant); only patients who have a successful result proceed to implantation [14].

In Oliver et al. [10], the patients were evaluated with both sacral nerve stimulation and pudendal afferent stimulation via the dorsal penile nerve or dorsal clitoral nerve. Although there was a difference in the volumes achieved at various urge levels, Wilcoxon paired testing revealed no other significant disparity between the techniques (Table 3). Stimulating pudendal afferent nerves noninvasively appears to be comparable to stimulating the mixed sacral nerve invasively at the sacral foramen, suggesting the possibility that dorsal penile/clitoral nerve stimulation may be a viable

**TABLE 1** Validation of the 'urge keypad': comparison of mean bladder volumes at sensation scores 1, 2 and 3 for 10 subjects

<table>
<thead>
<tr>
<th>Sensation score</th>
<th>Mean (SD) bladder volume, mL</th>
<th>N measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>110 (68)</td>
<td>237 (139)</td>
</tr>
<tr>
<td>2</td>
<td>164 (83)</td>
<td>284 (138)</td>
</tr>
<tr>
<td>3</td>
<td>234 (105)</td>
<td>334 (136)</td>
</tr>
<tr>
<td>4</td>
<td>302 (130)</td>
<td>371 (133)</td>
</tr>
</tbody>
</table>

*Bladder volume is given at each level of sensation with and with no neuromodulation by pudendal afferent nerve stimulation. Results are for patients in whom neuromodulation suppressed sensation. Bladder volumes (score 4) increased significantly from baseline but the greatest increases occurred at the two lowest scores. Other changes were significant for the difference between control and stimulated bladder volumes (Wilcoxon matched-pairs test). Indicates relative percentage increase in mean bladder volume from control to stimulation cystometrogram. Adapted with permission from Oliver et al. [1].
A focused evaluation of bladder sensations offers a potentially valuable new tool for assessing and managing disordered lower urinary tract function, and may presage a movement away from the detrusor muscle as the predominant focus of urodynamic investigations into OAB. A developing and comprehensive approach to the mechanisms of urinary tract sensation considers the interrelations between the entire upper and lower urinary tracts, from bladder to brain, back through renal neurohumoral control, urine production, and then on to bladder filling and emptying [23]; in this scheme, sensory mechanisms of the urothelium, sensory innervation of the bladder, relevant spinal pathways responsible for transmission of relevant impulses, and higher cortical sites in the hypothalamus, frontal cortex, and peri-aqueductal grey matter devoted to perception of bladder fullness are integrated components of a sensate, reflexive, neuroregulatory system.

Sensory innervation of the bladder is a critical component of this chain [23]. Urothelial tissues in the bladder have been shown to have dynamic properties, responding to distension, as well as to specific components [24] in experimental urothelial models in vitro [25] or in actual urine in people [26], with a cascade of intracellular signals, culminating in the release of ATP and other neurotransmitters, the activation of specialized receptors (purinoceptors; P2X3 ligands), and increased sensory nerve activity. This ‘dynamic urothelium’ [27] is not simply a barrier lining the bladder wall and sequestering urine; it is replete with precise physiological mechanisms that respond to a myriad of stimuli, such as urinary potassium, urinary sodium, stretch and osmolarity, to regulate sensory messaging in the suburothelial space [25]. These observations suggest intriguing directions for clinical research into factors that influence urgency, residing throughout the integrated urinary tract from the most distal lining of the bladder to higher levels in the CNS.

**FIG. 5.** Unpublished results of the test-retest reliability of the ‘urge keypad’ during two cystometric assessments ≈3 months apart in four patients (with SEM) (a). To allow for differences in maximum bladder capacity of each patient, the results were normalized to the bladder capacity at sensation level 4 in the absence of any treatment. (b) shows published results of the relation between scores from the ‘urge keypad’ during cystometry and those noted subjectively in voiding diaries associated with voided volumes at home by the same patients as in (a) (with SEM, four patients). To allow for differences in maximum bladder capacity of each patient, the results were normalized to the bladder capacity at sensation level 3 in the absence of any treatment. Level 3 was chosen here because most patients at home would void before reaching level 4. Each datum point on each graph is based on more than six individual measures of volume at each sensation score in each patient. Adapted with permission from Oliver et al. [22].
CONCLUSION

One of the essential components of OAB is urinary urgency, which is unevenly related to involuntary detrusor contraction. Urgency in OAB is only suggestive of underlying detrusor overactivity, and is not diagnostic [3]; subsequent cystometric evaluation of patients with urgency may show no unusual detrusor contractions, and there is a range of detrusor activity associated with a spectrum of clinical presentations. Consequently, standard urodynamic investigations focused on involuntary detrusor activity may show a poor correlation with symptoms. Alternative efficacy measures are desirable.

An objective measure of bladder symptoms is a key to the accurate evaluation of symptoms of OAB and would be invaluable in assessing subsequent management and response to therapy. The ‘urge keypad’, a useful technique for repeated measurement of bladder sensations arising during bladder filling, was designed to eliminate the possibility of prompting or bias. Use of this device during medium-fill CMG has confirmed that sensations follow a reproducible pattern that
is well correlated with bladder volume in individual subjects, beginning with the FDV and culminating at maximum bladder capacity with a strong or desperate desire to pass urine.

The utility of the ‘urge keypad’ has been validated for documenting improvements in LUTS after neuromodulation. The reliability, reproducibility and ability of this method to provide good correlation between CMG findings and patient symptoms gives it important advantages over techniques based on documenting involuntary detrusor contractions.

Assessing sensation and quantifying a sensation score via a patient-activated keypad device can offer a new approach for evaluating subjective sensations arising from the urinary tract, one that may provide a simplified, objective and potentially preferable method for directing and assessing patient care. This technique offers a useful way to assess the response to treatment and to identify patients with severe OAB symptoms who may benefit from neuromodulation (or other) therapy.

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Abbreviations: OAB, overactive bladder; FSF, first sensation of bladder filling; FDV, first desire to void; SDV, strong desire to void; CMG, cystometry; ATP, adenosine triphosphate; UDV, urgent desire to void.
INTRODUCTION

The ICS defines overactive bladder syndrome (OAB) as urgency, with or without urgency urinary incontinence (UUI), usually with frequency and nocturia [1]. Local pathological or metabolic factors are generally absent, and the aetiology is unknown [2]. The primary symptom of OAB is the strong, sudden and often unpredictable desire to urinate [1]. Because many, but not all, patients have UUI, patients with OAB constitute a broader population than those with UUI.

Current estimates of the prevalence and economic impact of OAB have been derived from results of the recent National Overactive Bladder Evaluation (NOBLE) programme, a telephone survey of 5204 community-dwelling adults [3]. Survey data indicate that OAB affects >34 million people in the USA. The estimated prevalence is similar among women (16.9%) and men (16.0%), but gender-specific prevalence differs substantially by severity of symptoms. In women, the prevalence of UUI and OAB ranges from 2% (aged 18–24 years) to 19% (aged 65–74 years), increasing markedly after age 44 years. In men, the prevalence of UUI and OAB ranges from 0.3% (aged 18–24 years) to 10.2% (aged ≥75 years) [3].

HEALTH-RELATED CONSEQUENCES

In addition to markedly impairing a person’s quality of life, OAB is associated with poorer health status, more visits to physicians, and increased health risks [4]. According to the NOBLE study, patients with OAB report more health problems, including diabetes and congestive heart failure, than do those without OAB [4]. In addition, multivariate analysis shows that patients with OAB have an average of 84% more yearly visits to a physician than do those without OAB (7.781 vs 5.597 visits; \( P < 0.05 \)).

One common finding associated with OAB is UTI (Table 1), which affects 21.7% of patients with OAB compared with 10.2% of those without OAB (\( P < 0.001 \)) [4]. On multivariate analysis, patients with OAB had =21% more UTIs annually than did those without OAB (\( P < 0.001 \)). The risk of UTI is higher in the elderly, women and patients with significant comorbidities such as heart disease, diabetes and other bladder problems. In addition, the presence of a UTI may predispose patients to develop various skin conditions related to incontinence [2]. Although an association between OAB and UTI has been established, further research is needed to determine the cause.

Patients with OAB also have a significantly greater risk of fall-related injuries (17.7%) than do those without OAB (8.9%; \( P < 0.001 \)) [4]. The risk of fall-related bone fracture (5.0% vs 2.7%) and the number of fall-related injuries (0.287 vs 0.163) tend to be higher in patients with OAB than in those without OAB. However, the reasons for this increased prevalence of fall-related injuries are not understood.

ECONOMIC CONSEQUENCES

According to an estimate derived from the NOBLE survey and various economic measures, the overall annual costs associated with OAB in the community setting are >$9 billion (Table 2) [5]. If the estimated $2.9 billion for the institutional cost of OAB is added to that figure, the total cost for OAB is >$12 billion annually in the USA. These figures include direct costs of treating both OAB and the related conditions described previously, as well as the indirect costs associated with lost productivity. Thus, the total costs for OAB are of the same magnitude as those for breast cancer ($12.7 billion) and the treatment costs for osteoporosis ($13.8 billion) [6]. However, the public’s awareness of the magnitude of OAB is far less than it is for well-publicized conditions such as osteoporosis.

Each year, ≈$4.4 billion is spent on the diagnosis and treatment of OAB in the community setting [5]. This economic burden of OAB varies by gender and age. For example, the costs of diagnosing OAB are higher in younger women (aged <65 years) than in older women (≥65 years). By contrast, more money is spent on home care and routine care in younger women than in older women. The costs of pharmacological treatment are similar for both older and younger women.
($554 million and $584 million, respectively) and older and younger men ($28 million and $31 million, respectively). However, the total spent for pharmaceutical treatment is markedly higher for all women ($1138 million) than for all men ($59 million). A similar variation between genders in other components of treatment-related costs is shown in Table 3. Even the costs of routine care are substantially higher in women ($1.3 billion) than in men ($248 million). Overall, the cost of diagnosing and treating OAB in the community is more than seven times higher for women ($3.9 billion) than for men ($533 million).

Economic analysis should also include the costs of health-related consequences of OAB. In 2000, almost $3.9 billion was spent on increased nursing-home admissions and longer hospital stays, as well as treatment of UTIs, broken bones, falls and UUI-related skin conditions (Table 3) [5]. A subanalysis showed cost discrepancies between men and women [5]; e.g. nursing home admissions, which account for more than half of the money spent on treating OAB-related conditions, were responsible for costs of almost $1.5 billion for women, compared with $493 million for men. Treatment of UTIs is another significant cost; in 2000, the figures were $1.2 billion for women and $186 million for men. Together, these conditions comprise >85% of the cost of the consequences of OAB. Overall, >$3 billion is spent on treating OAB-related conditions in women and >$824 million in men.

An indirect cost of OAB is the loss of productivity, including lost work time and interference with job performance. For women, the overall loss is estimated to be $400 million ($14 million for women aged ≥65 years and $386 million for those aged <65); for men, the calculated value is $441 million ($15 million for men aged ≥65 years and $426 million for those aged <65). Thus, the estimated total loss in terms of productivity is $841 million [5].

When all of the direct and indirect costs of OAB are added, the annual total is $9.2 billion for community residents [5]. On average therefore, $267 is spent annually for every patient with OAB; the cost/patient is $410 for women and $110 for men. The major cost differences are attributable to higher routine care (incontinence supplies), UTI incidence and nursing-home care among women.

**OUTSTANDING ISSUES**

Although the NOBLE study provided an excellent basis for estimating the prevalence and costs of OAB, more information is needed to calculate fully the costs of OAB. In particular, the costs of OAB over a lifetime should be determined, and these data should be analysed by gender. Obviously, such calculations would require incidence information, longer follow-up, and prospective analyses of long-term use of healthcare resources.

Another interesting topic for further exploration is the subgroup of patients with OAB including UUI (OAB-wet). An estimated 2.7 million patients fall into this category. The consequences and cost of having OAB-wet should be determined [7]. This special group could incur higher costs than are spent to treat patients with either OAB or UUI, e.g. stress incontinence. The prevalence of OAB without UUI reaches a plateau in women aged ≥64 years and ≥56 years for men; however, the prevalence of OAB-wet increases markedly, suggesting that OAB alone may precede OAB-wet. If this suggestion is confirmed by longitudinal studies, preventing UUI should be included in the treatment protocol for OAB [3].

From an economic perspective, investing more healthcare resources to improve initial treatment should reduce the costs of treating late-stage disease and its consequences. As described previously, the cost of diagnosing and treating OAB (= $2.9 billion) is less than the cost of treating its related consequences (= $3.9 billion).

Furthermore, the cost of treating OAB alone is less than that for treating OAB-wet, although more patients have OAB alone [7]. Thus, the cost subanalyses raise some important questions. First, would more effective treatment for OAB itself markedly reduce the incidence and costs of treating such health-related consequences as UTIs and injuries? Because UTIs comprise a significant portion of this expense, determining whether proper treatment of OAB reduces the incidence of UTIs is worth further evaluation. Second, would any increased cost of effective treatment for OAB be offset by a subsequent reduction in the costs of treating the health-related consequences? For example, assessing whether administration of treatment for OAB forestsalls admission to a nursing home would be an interesting investigation, albeit one difficult to conduct. Finally, would the increased cost of effective treatment be offset by improved productivity if patients are able to remain at work? The answers to these questions lie partly in establishing the underlying mechanisms that link OAB with increased risks of UTIs, falls and injuries; from clarification of any such causal link would...
emerge important targets for the development of cost-effective measures for preventing and treating OAB.

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Abbreviations: OAB, overactive bladder; UUI, urgency urinary incontinence; NOBLE, National Overactive Bladder Evaluation.