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Nocturia is more bothersome than daytime LUTS: Results from an Observational, Real-life Practice Database including 8659 European and American LUTS patients

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Summary

Purpose: Lower urinary tract symptoms (LUTS) encompass several diagnoses, including overactive bladder (OAB) and benign prostatic hyperplasia (BPH). Nocturia is a standalone symptom, but also included in OAB and BPH. Current discussion addresses whether the overlap of the diagnoses is too broad, leading to misdiagnosis. This study explored the differences in level, causes and consequences for patients with a diagnosis of daytime LUTS compared with a diagnosis of nocturia, and discussed whether people are being treated for the symptoms that truly bother them the most.

Patients and methods: Data were drawn from a survey of physicians and patients in France, Germany, Spain, UK and USA. Physicians filled out patient record forms (PRFs) for patients with LUTS diagnosis. The patients completed the patient self-completion form (PSC). Three PRO questionnaires were included; the OAB-q SF, NI-Diary and WPAI. Patients were grouped based on the diagnoses assigned to them by their physicians in a real-life setting.

Results: Eight thousand seven hundred and thirty eight patients had a LUTS diagnosis and 5335 completed a PSC. Patients diagnosed with night-time symptoms were significantly more bothered by their LUTS than only daytime LUTS patients (all questionnaires $P < .0001$). Patients with nocturia reported being tired "always" or "usually" more often than patients with daytime problems only ($P < .0001$). Only 13% of patients with nocturia had an initial sleep period of more than 2-3 hours.

Conclusion: In this population of real-life patients, those with a diagnosis of nocturia reported significantly higher impact on their quality of life than patients with a diagnosis of daytime LUTS only. The underlying causes of bother were related to sleep problems. It is essential that nocturia is understood, treated and monitored as a distinct problem from OAB and BPH, to ensure that patients are treated for their main symptom.

1 | INTRODUCTION

The field of lower urinary tract symptoms (LUTS) consists of several broad and symptom-based diagnoses, including OAB and BPH, which encompass various underlying aetiologies. There is currently an ongoing discussion as to whether the BPH and, in particular, the OAB diagnosis are too all-encompassing and reliant on symptomology, leading to a high level of misdiagnosis and inappropriate treatment.[1]

Nocturia was recognised by the International Continence Society (ICS) as a standalone symptom in 1999 and defined as"… the complaint that the individual has to wake at night one or more times to void."[2] However, nocturia is also part of the definition of the OAB syndrome, and in 2010 the ICS stated its definition as a condition with characteristic symptoms of "urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology."[3,4] In the gold-standard diagnostic tool for BPH, the International Prostate Symptom Score (IPSS), there is an optional question on nocturia ("How many times did you typically get up at night to urinate?")

Qualitative studies of the impact of LUTS on patients have revealed that some areas of complaint are shared between OAB, BPH and nocturia whereas other areas seem to be quite distinct and specific to the different conditions.[5,6] For example, while the number of voids impacts on the bother experienced by patients with OAB, BPH and nocturia, new studies suggest that the bother associated with nocturia is more directly related to its effect on sleep.[7,8] The consequences that nocturia has for quality of life are probably more closely associated with parameters such as the hours of undisturbed sleep before the first void or the ability to fall back to sleep after visiting the toilet, than with the actual urological symptoms.[9,10]

The aim of this study was to explore the differences in level, underlying causes and consequences of the impact of daytime LUTS vs nocturia to discuss whether patients are being treated for the symptoms which trouble them the most in real life.

What's known

- It is well established that OAB and BPH are both very broad diagnoses, where the treatment satisfaction is limited.

What's new

- This article documents that real-life diagnoses within the area of LUTS are largely overlapping, not aligned with actual symptoms and not adapted to the main cause of bother to the patient. LUTS increases significantly with age and thus many elderly patients are receiving medical treatment for a symptom that does not bother them significantly, while the bothersome symptoms persist.

2 | MATERIAL AND METHODS

Data were drawn from the LUTS Disease-Specific Programme (DSP®), a cross-sectional, real-world, multinational survey of physicians (primary care (PCP), urologists and gynaecologists) and their consulting patients in France, Germany, Spain, the UK and the USA. Thus, the current study reflects how patients are diagnosed in real life when they visit the physicians, as opposed to more traditional retrospective surveys where the analysis is based on a theoretical framework. The diagnoses discussed in this paper are the diagnoses applied by the physicians in real life and have not been changed for analytical purpose by the authors.

The survey was conducted in accordance with the European Pharmaceutical Market Research association 2012 code of conduct for international healthcare market research and the US Health Insurance Portability and Accountability Act 1996.[11] Patients had to provide consent for reporting of research findings as required. Data were collected by local fieldwork partners and fully anonymised. Target physicians were identified by the local fieldwork team from public lists of healthcare professionals. All physicians had to have been qualified for between 3 and 35 years. Primary care physicians and urologists had to be consulted by 4 or more BPH patients and 3 or more OAB patients a week on average; gynaecologists had to be consulted by 6 or more OAB patients a week on average. A full description of the methodology has been published previously.[12]

The survey was conducted in February-May 2013. During the survey, physicians completed a patient record form (PRF) for the next 14 consecutively consulting patients whose diagnosis included BPH, and/or OAB, and/or nocturia/nocturnal polyuria. The PRF included details of the confirmed diagnosis following evaluation. The diagnosed patients were invited to fill out the patient self-completion form (PSC) incorporating a number of validated questionnaires on the impact of LUTS as detailed below. The overall aim of the PSC was to assess the degree of level, underlying causes and impact of LUTS. In the PSC, the patient detailed the numbers of voids over the previous 7 nights and questions around sleeping pattern. This was followed by an overall question on the time of day patients predominantly experienced their urinary problems. The LUTS Disease-Specific Programme is a non-interventional survey of real-life clinical practice and does not require patients to be tested or otherwise investigated specifically for the survey.

2.1 | Patient-reported outcomes

The three PRO questionnaires used in the study were the Overactive Bladder-Questionnaire Short Form (OAB-q SF), the Nocturia Impact Diary (NI-Diary) and the Work Productivity and Activity Impairment (WPAI) questionnaire. They are all frequently used and assess different aspects of impact on the patient.

2.1.1 | The Overactive Bladder-Questionnaire Short Form

The OAB-q SF is a reduced version of the OAB-q, designed to assess patient perception of symptom severity and impact on health-related quality of life (HRQoL) in OAB.[13] It includes a 6-item symptom severity scale and a 13-item HRQoL scale. Both scales have a range of 0-100, however, a higher score on the symptom severity scale indicates greater symptom severity or bother, while a higher score on

the HRQoL scale indicates better quality of life. The questionnaire has a 4-week recall period and the responses are rated on a 6-point scale ranging from "not at all" to "a very great deal". Two of the questions are directly related to nocturia.

For evaluation of the underlying causes of symptom severity and bother, the 6 items of the OAB-q SF symptom severity score were collapsed to dichotomous scales of "not bothered" (responses 1-3) and "bothered" (responses 4-6).

2.1.2 | The Nocturia Impact Diary

The NI-diary is a 12-question disease-specific nocturia scale assessing the impact of nocturia on patients' lives.[14] It includes an 11-item scale assessing the daily impact of nocturia and a single question assessing the overall impact of nocturia. Both scales have range of 0-100 with a higher score indicating greater impact. It is a re-validated and improved version of the disease-specific N-QoL (nocturia QoL). It was developed to be used in conjunction with a voiding diary. Responses are on a 5-point scale ranging from "not at all" to "a great deal."

2.1.3 | Work Productivity and Activity Impairment

The WPAI measures the impact of a given disease on activity impairment and work productivity and is widely used for this purpose.[15] The WPAI questionnaire is a self-administered questionnaire with 6 items that investigate 4 aspects of disease impact on patients: absenteeism (work time missed), presenteeism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment; derived from both absenteeism and presenteeism) and activity impairment (impairment outside of work). The WPAI outcomes are expressed as impairment percentages on a 0%-100% scale, with higher numbers indicating greater impairment and less productivity.

2.2 | Patient subgroups

The patients were grouped based on physicians actual real-life diagnosis (and were not changed or adapted to fit guidelines afterwards):

1) Patients where only the term nocturia or nocturnal polyuria (NP) occurred in the diagnosis
2) Men where the term nocturia or NP appeared in the diagnosis with either BPH or OAB
3) Men where only the term BPH or OAB occurred in the diagnosis
4) Women where both the term OAB and nocturia or NP occurred in the diagnosis
5) Women where only the term OAB occurred in the diagnosis.

Patients were also grouped as follows:

1) Patients with any type of night-time problem (groups 1, 2 and 4 above)
2) Patients with daytime problems only (groups 3 and 5 above)

2.3 | Statistics

All analyses were performed in Stata v14.1 or higher.[16] Significance was assessed using Mann-Whitney *U* tests for numeric outcomes (because of their non-parametric distribution) and Fisher's exact tests or Pearson's Chi-squared tests for categorical data. Any patients with missing values for a particular variable were removed from all pieces of analysis where that variable was used; however, those patients were still eligible for inclusion in other analyses. The number of patients/physicians providing a response to each question in the PRF/PSC is expected to vary because of imperfect physician knowledge, patients' unwilling answer to a particular question etc.

3 | RESULTS

3.1 | Patient demographics and number of voids

A total of 627 physicians (261 primary care physicians, 106 gynaecologists and 260 urologists) completed PRFs, including details of the diagnosis, for 8659 patients, of which 5291 (61%) completed a PSC (Figure 1).

Five hundred and seventy-six (7%) patients were diagnosed with nocturia only; 1060 men (12% of total sample; 21% of men) were diagnosed with nocturia and BPH/OAB and 3849 men (44% of total sample; 75% of men) with BPH/OAB only. Most women (2566, 30% of total sample; 73% of women) were diagnosed with OAB only and only 608 (7% of total sample; 17% of women) with

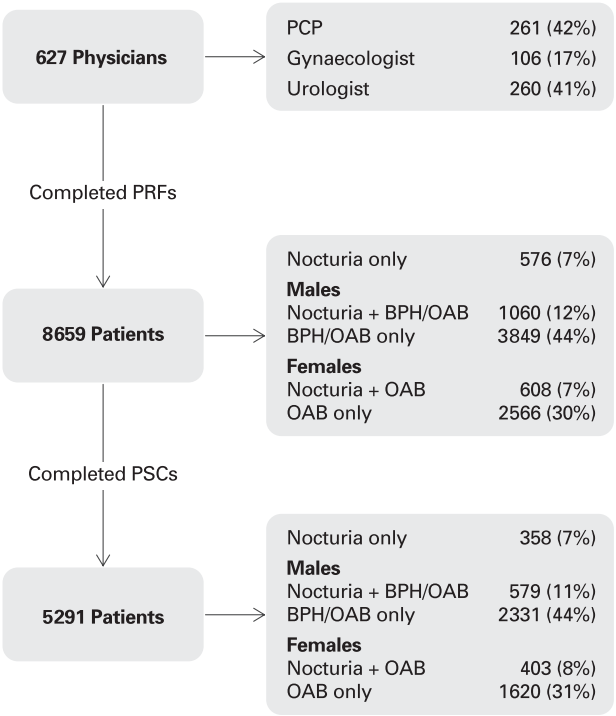

FIGURE 1 Patient flow diagram

nocturia and OAB. A total of 2244 patients (26%) had a physician-confirmed diagnosis of nocturia as recorded by the physician in the PRF.

The number of patients who completed a PSC in each diagnosis group was: nocturia only (358), men with nocturia and BPH/OAB (579), men with BPH/OAB only (2331), women with OAB only (1620), women with nocturia and OAB (403).

The mean age of patients was 64, 60% were men and the mean BMI was 27.4 (Table 1). Most patients (71%) were living with their partner; only 32% of patients were employed, whilst 54% were retired. Patients reported an average of 7.5 daytime voids and 2.5 night-time voids. Physicians seemed to underestimate the number of daytime voids (mean 6.6) compared with patient reports, but agreed with the patients on the number of night-time voids (mean 2.4). Interestingly, all patient groups suffered from nocturia as a symptom, even patient subgroups without a nocturia diagnosis, although this was more pronounced in the patient groups with nocturia as part of the diagnosis (3.3-3.7 voids/night according to patient reports compared with 2.0-2.4 voids/night for those without a nocturia diagnosis).

3.2 | Level of impact

Mean scores on the OAB-q SF, the NI-Diary and the WPAI are stratified by all patient subgroups in Figure 2. Patients diagnosed with nocturia felt significantly more impacted than patients diagnosed with daytime only LUTS in all scales ($P < .0001$). Unsurprisingly, this result was most pronounced for the NI-Diary (a nocturia specific scale). As seen in other studies using the WPAI, the productivity level was less impaired than the activity level. On every scale, women with nocturia and daytime symptoms had the worst outcomes of all the diagnostic subgroups.

3.3 | Underlying causes of impact

Patients diagnosed with nocturia were significantly more likely to report feeling impacted by their symptoms than patients with daytime LUTS (Figure 3).

Both male and female patients with a nocturia diagnosis reported feeling more bothered by daytime problems (uncomfortable urge to urinate, a sudden urge to urinate, accidental loss of urine, urine loss associated with a strong urge to urinate) than male and female patients without a nocturia diagnosis. As expected, more patients with a nocturia diagnosis reported being bothered by night-time symptoms (night-time urination and waking to urinate) than patients without a nocturia diagnosis.

Most patients with a nocturia only diagnosis (78%) experienced their urinary problems predominantly during sleeping hours. However, 40% of the women and 66% of the men diagnosed only with daytime problems stated that their LUTS problems were experienced predominantly during sleeping hours or equally during waking and sleeping hours.

TABLE 1 Patient demographics and number of day- and night-time voids reported by physicians and patients

	All Patients (n = 8659, ♀ = 3494, ♂ = 5165)	Nocturia only (n = 576. ♀ = 320, ♂ = 256)	Men Nocturia + BPH/OAB (n = 1060)	Men BPH/OAB only (n = 3849)	Women Nocturia + OAB (608)	Women OAB only (n = 2566)
Mean age (y)	64	61	68	67	61	59
Men	60%	44%	100%	100%	0%	0%
BMI	27.4	27.5	28.0	27.4	27.6	27.1
Live with partner	71%	66%	72%	74%	67%	69%
Employed	32%	35%	29%	29%	27%	40%
Retired	54%	46%	67%	67%	41%	32%
Number of daytime voids reported by physician (PRF)	6.6	5.2	6.3	6.4	7.0	7.3
Number of daytime voids reported by patient (PSC)	7.5	6.4	7.4	7.2	7.9	8.0
Number of nocturnal voids reported by physician (PRF)	2.4	3.6	3.2	2.3	3.3	1.9
Number of nocturnal voids reported by patient (PSC)	2.5	3.7	3.3	2.4	3.3	2.0

Patient self-completion form (PSC), patient record form (PRF).
$P < .0001$ for each outcome across all patient subgroups.

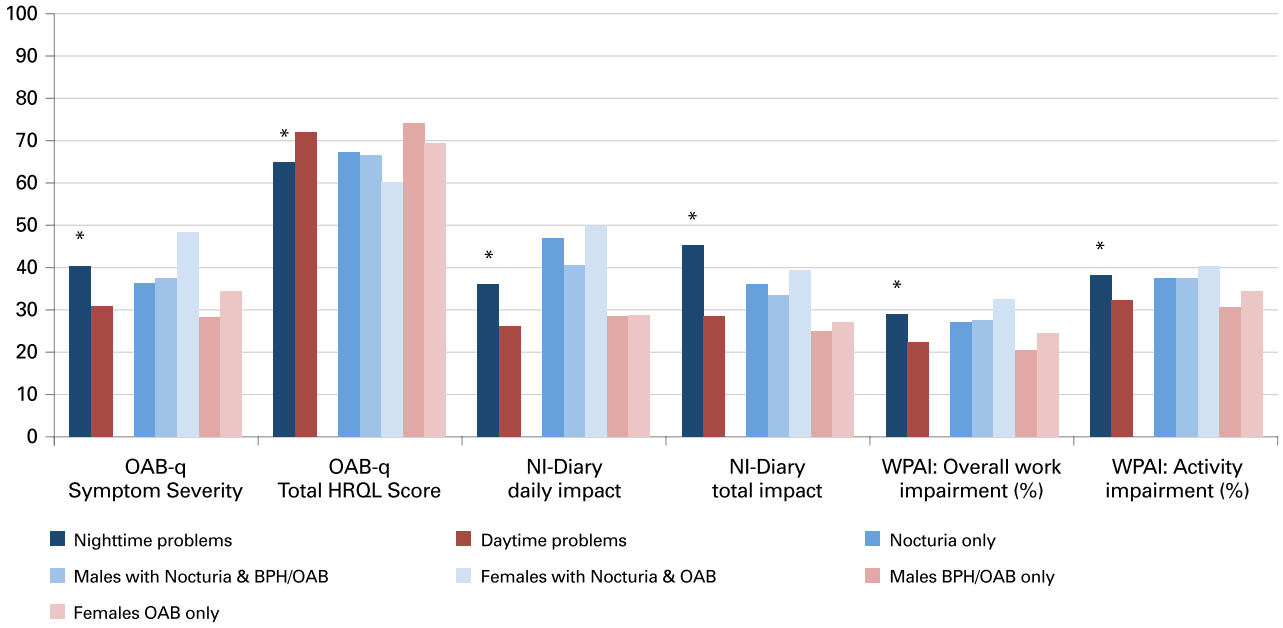

FIGURE 2 Impact of LUTS as measured by the OAB-q SF, the NI-Diary and the WPAI. *$P < .0001$ between daytime problems and night-time problems

3.4 | Consequences of impact

In the survey, 60% of patients diagnosed with night-time problems reported being tired "always" or "usually"; this proportion was significantly lower (37%; $P < .0001$) for patients with daytime problems only.

Only 11% of nocturia only patients, 14% of male nocturia + BPH/OAB patients and 12% of female nocturia + OAB managed to sleep more than 2-3 hours before waking up, whereas 28% of women with OAB only and 29% of men with BPH/OAB only had more than 2-3 hours of undisturbed sleep ($P < .0001$) (Figure 4).

In all diagnostic categories, a large proportion of patients reported that they "always" or "usually" had difficulty getting back to sleep after going to the toilet at night. There was a greater tendency for patients with nocturia in their diagnosis to experience this problem (61% nocturia only, 54% men with nocturia + BPH/OAB, 65% women with nocturia + OAB) than those with daytime symptoms only (46% men BPH/OAB, 55% women OAB only).

4 | DISCUSSION

This study sought to dissect the level, underlying causes and consequences of LUTS during day or night-time (ie, nocturia) in a group of patients actively seeking help for their urological problems. It was demonstrated that night- and daytime urinary problems indeed impact patients' lives negatively, but a diagnosis of nocturia has significantly more impact on a patient's daily living than a diagnosis of daytime LUTS. A key finding of this study was that nocturia is associated with a specific set of underlying

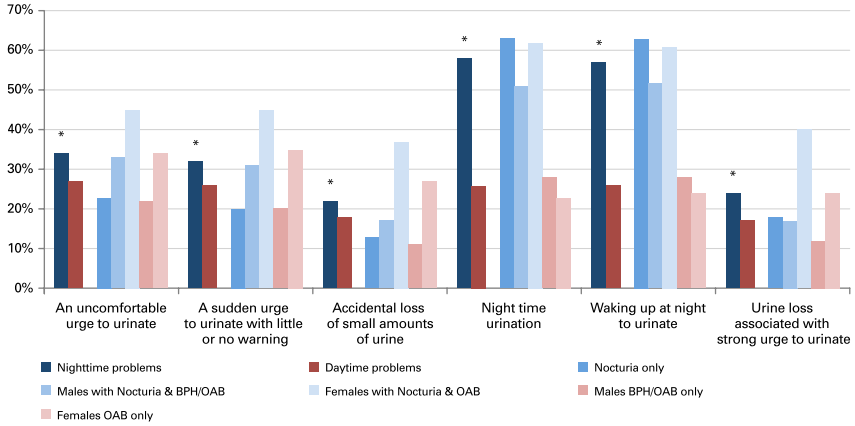

FIGURE 3 LUTS impact on typical day- and night-time bother. *$P < .001$ between daytime problems and night-time problems

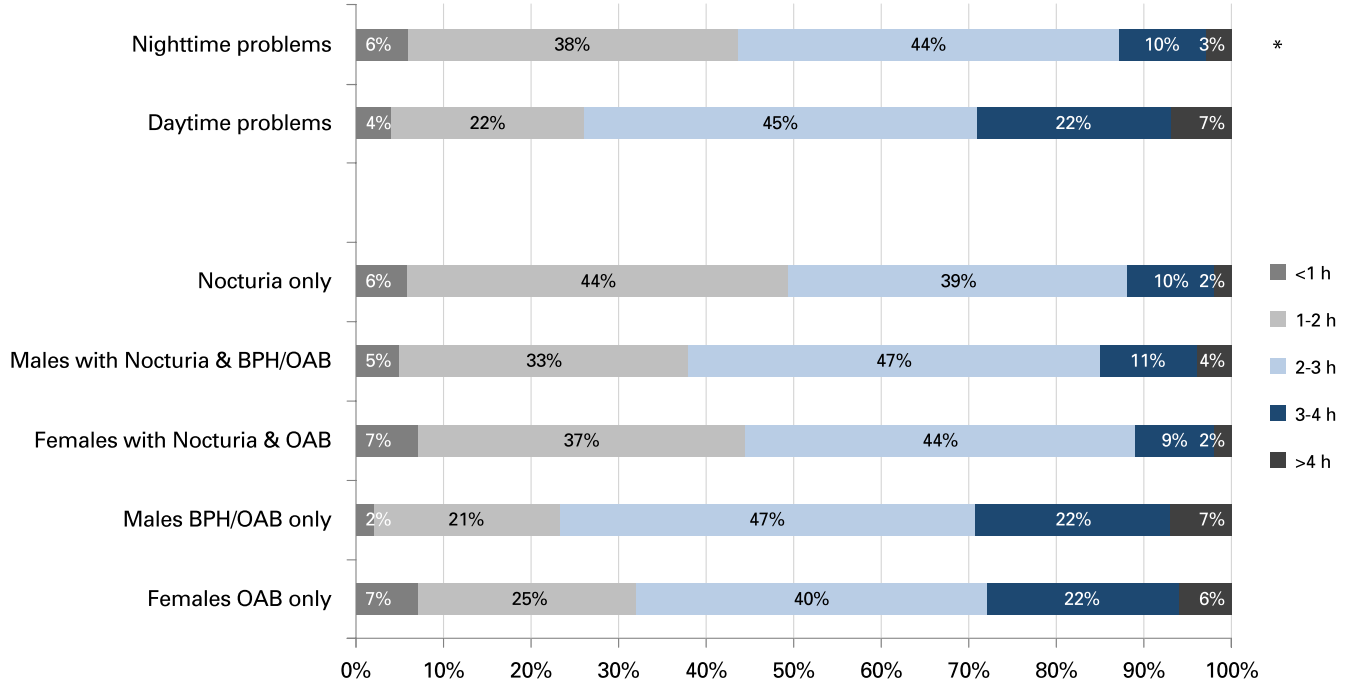

FIGURE 4 How long after you fall asleep, do you usually wake up wanting to pass urine? *P < .0001 between daytime problems and night-time problems

problems strictly related to sleep, such as feeling tired frequently and having a short initial period of sleep. These findings correspond well with other studies related to the consequences of nocturia.[5,17]

Patients in this study, who were not diagnosed with nocturia, surprisingly experience approximately 2 voids per night, raising the question whether they did not feel bothered about nocturia or whether nocturia was absorbed in the broad daytime LUTS diagnosis.

All groups reported difficulties getting back to sleep after a night-time visit to the toilet. This might be a key issue when trying to understand the difference in day- and night-time LUTS and the severity of the consequences of nocturia.[9,10,18]

These findings are important for the clinic, because they highlight the problems of using non-specific diagnoses of OAB and BPH to incorporate nocturia as well as daytime symptoms. When these quite distinct problems are integrated under the same diagnostic umbrella term, there is a risk that the main underlying causes of impact (ie, night-time voiding and sleep difficulties) experienced by the patient will be overlooked.

It has been reported that physicians tend to underestimate the impact of moderate nocturia.[19,20] The findings of this study may provide some clues as to the reasons behind this, given that physician focus is traditionally on urological symptoms (ie, the number of voids), whereas patient concerns relate more strongly to the amount and quality of sleep. In particular, LUTS doctors seldom enquire about patients' ability to get back to sleep — a key difficulty for a high proportion of individuals with nocturnal voiding in this study. We suggest that it may, therefore, be more relevant for physicians to diagnose nocturia and monitor treatment benefit by evaluating sleep end-points rather than simply number of voids.

This study is limited by the fact that the data on impact are all derived from patients with LUTS, and no comparison with the general population is included. As such, it is impossible to view the level of impact and sleep problems in the context of issues reported by the wider non-LUTS population. In addition, the NI-Diary, which was included as one of the tools in this study, is validated for patients with pure nocturia as well as mixed symptoms, but not for pure daytime symptoms. This is likely reflected in the low impact scores derived from the NI-Diary for patients without nocturia. However, as the same pattern of impact across diagnostic subgroups was seen using the OAB-q SF and WPAI questionnaires, this is unlikely to have affected our results substantially.

Across all outcomes described, the observed findings remained consistent when stratified by patients consulting the individual physician types, with the exception of patients consulting a gynaecologist. These particular results may have differed from the observed findings because of the predominantly female patients with an OAB only diagnosis that were recruited by the gynaecologists as part of the DSP.

5 | CONCLUSION

In this population of real-life patients, those who got a diagnosis of nocturia reported significantly higher levels of impact on their lives than their counterparts with a diagnosis of daytime LUTS only. The underlying cause of impact was related to sleep problems such as the lack of undisturbed sleep. More than half of the men and 40% of the women

who were diagnosed with OAB or BPH and no nocturia, stated that they experienced their main LUTS problem predominantly at night or equally day and night. Hence, this study underlines the need for more precision in the diagnosis of LUTS and for nocturia to be understood, treated and monitored as a different problem to OAB and BPH to ensure that patients are treated for their most troublesome symptom.

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AUTHOR CONTRIBUTIONS

Everaert K, data analysis, manuscript writing/editing; Anderson P, protocol/project development, data collection or management, manuscript writing/editing; Andersson FL, protocol/project development, data analysis, manuscript writing/editing; Holm-Larsen, T, protocol/project development, data analysis, manuscript writing/editing.

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