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Impact of nocturia on patients' health-related quality of life and healthcare resource utilisation compared with OAB and BPH: Results from an observational survey in European and American patients

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Abstract

Objective: To evaluate the impact of nocturia on patients' quality of life and healthcare resource utilisation (HRU) compared with overactive bladder (OAB) and benign prostatic hyperplasia (BPH).

Methods: Data were drawn from a multinational (France, Germany, Spain, UK and US) survey of physician and patient-reported outcomes. The patient groups of interests were those diagnosed with only nocturia, with only OAB, and with only BPH. Health-related quality of life (HRQoL) and productivity measures were derived from the EuroQoL-5D, OAB-q and the Work Productivity and Activity Impairment Questionnaire (WPAI). Measures of HRU included lower urinary tract symptoms (LUTS)-relevant surgeries, hospitalisations, current use of pads and related physician visits. Bivariate and multivariate regression analyses were used to evaluate associations between HRQoL/HRU/Productivity and nocturia status. Multivariate analysis was used to address any potential confounding factors among the groups, ie age, gender, body mass index (BMI), ethnicity and comorbidities.

Results: A total of 3552 patients were identified including 358 nocturia patients, 1415 OAB patients and 1779 BPH patients. The mean age of the nocturia patients was 61.2 years with a mean BMI of 27.3. About 60.6% were women, 87.2% were Caucasian, and their most common comorbidities included depression, hypertension and diabetes. In terms of impact, nocturia patients were significantly worse off than OAB patients in their HRQoL. There was no significant difference regarding HRU and productivity measurement. Nocturia patients also presented with significantly worse HRQoL and lower productivity compared with BPH patients. Nocturia patients also had more physician visits.

Conclusions: Nocturia should be emphasised as a standalone LUTS disease with substantial patient impact. Compared with OAB and/or BPH, nocturia patients presented

with a significant reduction on patients' quality of life, reduced work productivity and increased utilisation of healthcare resources.

1 | INTRODUCTION

Nocturia is a common yet under-reported lower urinary tract symptoms (LUTS) condition.[1] Recognised by the International Continence Society (ICS) as a standalone condition in 1999, nocturia is defined as the condition when an individual has to wake at night to void one or more times, with each of the voids followed by sleep.[2] However, recent studies suggest that two voids per night is the threshold beyond which nocturia is burdensome and associated with impaired quality of life[3,4] and this definition is used in this study.

Nocturia is often associated with or caused by nocturnal polyuria (NP), the excessive production of renal urine during the night.[5] Current treatments for the more widely diagnosed overactive bladder (OAB) and benign prostatic hyperplasia (BPH) aim to increase bladder capacity and/or lower bladder outlet obstruction, but these do not always effectively treat those patients suffering from nocturia.[1,5] Nevertheless, nocturia is increasingly recognised as one of the most bothersome symptoms for those suffering from LUTS,[6] and the leading cause of sleep disturbance.[6,7] The sleep fragmentation experienced by individuals with nocturia can severely impact their sleep quality and daytime energy level, and negatively impact their health-related quality of life (HRQoL) and work productivity.[8,9]

There has been an ongoing discussion on involving the patients' voice and preferences during the development of medical products.[10] Regulatory agencies (for example, the US Food and Drug Administration) and health technology assessment bodies (such as the UK's National Institute for Health and Care Excellence [NICE]) have increasingly adopted new policies to assess the value of new products based on real-world patient-reported outcomes.[10-12] For patients suffering from LUTS, previous studies conclude that some HRQoL measures are quite distinct and specific to different symptoms.[6] However, there is a lack of clear evidence showing the difference on quality of life and healthcare resource utilisation (HRU) among all the LUTS conditions, especially when comparing nocturia with the more broadly diagnosed OAB and BPH.

The aim of this analysis was to compare nocturia patients with OAB and BPH patients with regards to HRQoL, productivity and HRU, and assess whether the disease and societal burden of nocturia is significantly different to that observed for OAB and BPH.

What's known

- The negative impact of nocturia (waking up at night to void two or more times) on patients' quality of life (QoL), healthcare use and productivity has been well documented, also compared with other lower urinary tract symptoms diagnoses.
- These studies have generally used mixed populations, eg. overactive bladder (OAB) plus nocturia or benign prostatic hyperplasia (BPH) plus nocturia, as they may be overlapping or even difficult to separate.

What's new

- This real-life, multivariate study tries to discern the impact on single-diagnosis patients, ie nocturia-only, benign BPH-only and OAB-only patients.
- Compared with OAB patients, nocturia patients present with lower health-related QoL, whereas compared with BPH patients, nocturia patients present with lower overall QoL as well as worse work and activity impairments.
- The negative impact coming from nocturia is thus even larger than estimated before.

2 | PATIENTS AND METHODS

This analysis was conducted using the LUTS Disease Specific Programme (DSP™), a multinational survey undertaken in the UK, France, Germany, Spain and the US in 2013. The DSP is a large-scale real-world cross-sectional survey of LUTS patients and their treating physicians. The detailed methodology of this type of survey has been published.[13] The survey includes patient self-reported data including patient demographics, quality of life, management of disease, and productivity, as well as physician-reported data focusing on treatment practice and healthcare utilisation (see Table 1).

The data utilised in this study were collected from 635 physicians (primary care physicians, gynaecologists and urologists) and 8738 consulting patients with a physician-confirmed LUTS diagnosis. During the survey, physicians completed a patient record form for the next 14 consulting patients, who were diagnosed with one or any combination of OAB, BPH, nocturia and/or NP. The same patients were then invited to fill out a patient self-completion form (PSC), which recorded patient-reported outcomes (PROs) including the EQ-5D-5L, the OAB Questionnaire (OAB-q) and Work Productivity and Activity Impairment (WPAI).[14-16] Patients were not tested or investigated prior or during the survey and their questionnaire responses were not seen or influenced by their physician.

The DSP was conducted in accordance with the European Pharmaceutical Market Research Association code of conduct for international healthcare market research[17] and the US Health Insurance Portability and Accountability Act 1996. Patients were required to sign the informed consent to agree on anonymously

TABLE 1 Data source characteristics

	DSP (n = 8738)
Year of data collection	2013
Survey type	Cross-sectional
Respondent	Patient-reported outcomes, with clinical data collected from physicians, self-reported completion method
Patient-reported outcome	EQ-5D-5L, WPAI, OAB-q
Physician-reported outcome	HRU
Confounding covariates	Demographics, comorbidities, drugs prescribed, health/lifestyle indicators, income, home circumstances, treatment history, physician-reported outcomes
Geography	UK, France, Germany, Spain, USA

Abbreviations: DSP, Disease Specific Programme; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; HRU, Health Resource Utilisation; OAB-q, overactive bladder questionnaire; WPAI, Work Productivity and Activity Impairment.

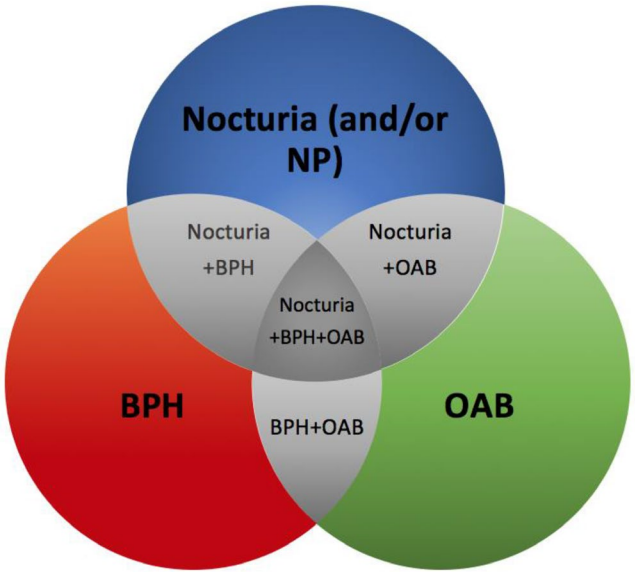

FIGURE 1 Patients' diagnosis. The selected patient samples are highlighted in blue, red and green. The grey zones indicate the population excluded from the analysis

reporting research findings as required. Data were collected by local partners who ensured compliance with patients' privacy. Ethical approval was not required for this type of survey, because the aim was to improve understanding and not to test any hypotheses or treatments. Clinical practice should not be affected by the survey.

Since the DSP contains a large pool of patient data, three standalone patient groups were selected for this study: nocturia-only, OAB-only and BPH-only. The selection ensured that patients diagnosed with multiple conditions were excluded. For instance, the BPH-only group would not contain patients diagnosed with BPH mixed with OAB (*BPH + OAB*), BPH mixed with nocturia (*BPH + Nocturia*) and a mixture of BPH, OAB and nocturia (*BPH + OAB + Nocturia*). Since NP is often associated with nocturia and there were only 34 NP-only patients (without a co-diagnosis of nocturia), they were included in the nocturia-only group. The nocturia-only group therefore includes patients with nocturia and/or NP. The Venn diagram (Figure 1) illustrates the composition of those patient groups included in the analysis.

TABLE 2 Outcome measurement, score range and interpretation

	Outcome measures	Score range	Interpretation
HRQoL	EQ-5D utility score	−0.56 to 1.00	The higher the score, the better quality of life
	EQ-5D VAS	0-100	
	OAB-q symptom severity score	0-100	The lower the score, the better quality of life
	OAB-q HRQoL total score	0-100	The higher the score, the better quality of life
Productivity (WPAI)	Activity impairment (%)	0-100	The higher the percentage, the lower productivity
	Work time missed (%)	0-100	
	Impairment whilst working (%)	0-100	
	Overall work impairment (%)	0-100	
	Whether employed	Yes or no	N/A
Healthcare Resource Utilisation[a]	LUTS-related surgery	Yes or no	
	Hospitalisation in the last 12 mo	Yes or no	
	Current use of pads	Yes or no	
	Number of pads (if used)	0-80	The higher number of pads, the more HRU
	Number of physician visits in the last 3 mo	1-24	The higher number of visits, the more HRU

Abbreviations: EQ-5D, EuroQoL 5 Dimension; HRQoL, health-related quality of life; HRU, Health Resource Utilisation; LUTS, lower urinary tract symptoms; OAB-q, overactive bladder questionnaire; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.
[a]Among all factors of HRU, LUTS-related surgery, hospitalisation data were derived from the physician-filled patient record forms (PRFs). The information about current use of pads and number of physician visits was collected from the patient self-completion form.

To evaluate associations between HRQoL/HRU and nocturia status, bivariate and multivariate analyses were used. For the bivariate analyses, Student's *t* tests, chi-squared tests and Fisher's exact tests were used, depending on the type of variable being assessed.

For the HRQoL, multivariate analysis was used to address any potential confounding between the two groups, ie other factors (apart from nocturia status) that may bias the results. In particular, regression analysis was used. The type of regression was chosen depending on the type and distribution of the dependent variable. The coefficients and *P*-values for the group variable showed how the OAB-only and BPH-only groups compared with the nocturia-only group. The significance level was $P < .05$, and the significant values were highlighted when necessary.

Three categories of outcomes were examined in the multivariate analysis, referring to PROs and HRU measurement. PROs which measured HRQoL included the EuroQoL-5D utility score, derived from a combination of 3L tariffs (from each country's value set) and the 3L/5L crosswalk[18] and the EQ-5D visual analogue scale (VAS). More disease-specific instruments included the OAB-q symptom severity score and OAB-q HRQoL total score.

Productivity was assessed using the WPAI Specific Health Problem questionnaire.[16] More specifically, the WPAI questionnaire was adapted to LUTS in order to reflect the impact on those patients' employment, absenteeism and presentism. Patients were also asked about their overall activity impairment.

HRU was estimated via both physician-reported measures (physician visits, proportion of patients who ever had LUTS-related surgery; proportion of patients with LUTS-related hospitalisation over the past 12 months) and patient-reported measures (proportion of patients using pads at the time of PSC completion; number of pads used per week).

Possible score range and score interpretation pertaining to the outcomes measures derived from each instrument are listed in Table 2.

The quality of life outcome measures and health resource utilisation level for each of the three patient groups were analysed using bivariate analysis. In order to compare the results of the nocturia-only

TABLE 3 Patient characteristics

	Overall	OAB-only	BPH-only	Nocturia-only
Country, n (%)*				
Total	3552 (100)	1415 (39.8)	1779 (50.1)	358 (10.1)
France	761 (21.4)	328 (23.2)	389 (21.9)	44 (12.3)
Germany	676 (19.0)	302 (21.3)	288 (16.2)	86 (24.0)
Spain	902 (25.4)	284 (20.1)	505 (28.4)	113 (31.6)
UK	537 (15.1)	200 (14.1)	285 (16.0)	52 (14.5)
US	676 (19.0)	301 (21.3)	312 (17.5)	63 (17.6)
Age, y				
Mean (SD)*	63.6 (12.3)	58.9 (13.3)	67.8 (9.1)	61.2 (14.2)
Gender, n (%)				
Male*	2105 (59.3)	185 (13.1)	1779 (100.0)	141 (39.4)
Female*	1447 (40.7)	1230 (86.9)	0 (0.0)	217 (60.6)
Ethnicity, n (%)				
White/Caucasian	3104 (87.4)	1230 (86.9)	1562 (87.8)	312 (87.2)
Hispanic/Latino	149 (4.2)	64 (4.5)	70 (3.9)	15 (4.2)
Afro-Caribbean	145 (4.1)	55 (3.9)	78 (4.4)	12 (3.4)
Other	154 (4.3)	66 (4.7)	69 (3.9)	19 (5.3)
Selected comorbidities, n (%)				
Depression/anxiety/other psychological/psychiatric symptoms*	716 (20.2)	403 (28.5)	211 (11.9)	102 (28.5)
Hypertension*	1563 (44.0)	466 (32.9)	960 (54.0)	137 (38.3)
Diabetes*	572 (16.1)	177 (12.5)	316 (17.8)	79 (22.1)
BMI				
N[a]	3286	1316	1629	341
Mean (SD)*	27.2 (4.6)	26.9 (5.3)	27.5 (3.7)	27.3 (5.0)

Abbreviations: BMI, body mass index; BPH, benign prostatic hyperplasia; OAB, overactive bladder.
[a]BMI could not be calculated for 266 patients.
*$P < .05$ using chi-squared test or student's *t* test.

TABLE 4 Bivariate analysis on HRQoL, productivity and HRU

	Overall	OAB-only	BPH-only	Nocturia-only	*P* value
HRQoL					
EQ-5D-5L state valuation					.0611
N	3463	1373	1739	351	
Mean (SD)	0.85 (0.18)	0.85 (0.19)	0.85 (0.18)	0.83 (0.18)	
Median	0.91	0.91	0.91	0.88	
EQ-5D VAS					.0001
N	3421	1355	1717	349	
Mean (SD)	**74.2 (15.6)**	**74.4 (16.1)**	**74.6 (15.1)**	**70.8 (16.0)**	
Median	75.0	75.0	75.0	70.0	
OAB-q symptom severity					<.0001
N	3392	1352	NA	339	
Mean (SD)	**29.9 (18.7)**	**33.4 (19.7)**		**36.3 (17.4)**	
Median	26.7	30.0		33.3	
OAB-q total HRQoL score					<0.0001
N	3431	1372	NA	350	
Mean (SD)	**27.3 (17.4)**	**30.2 (17.6)**		**32.8 (16.8)**	
Median	26.2	29.2		30.8	
Productivity					
% Employed, n (%)					<.0001
N	3435	1363	1724	348	
Employed	**2318 (67.5)**	**817 (59.9)**	**1265 (73.4)**	**236 (67.8)**	
Unemployed	**1117 (32.5)**	**54.6 (40.1)**	**459 (26.6)**	**112 (32.2)**	
% work time missed					.3150
N	919	440	381	98	
Mean (SD)	2.6 (11.1)	2.7 (10.5)	2.9 (12.8)	1.0 (3.7)	
Median	0.0	0.0	0.0	0.0	
% impairment while working					<.0001
N	994	481	407	106	
Mean (SD)	**21.4 (20.3)**	**23.5 (21.0)**	**17.7 (18.4)**	**26.4 (21.7)**	
Median	20.0	20.0	10.0	20.0	
% overall impairment					<.0001
N	901	430	375	96	
Mean (SD)	**22.5 (22.0)**	**24.9 (22.8)**	**18.6 (20.3)**	**27.2 (22.4)**	
Median	20.0	20.0	10.0	23.2	
% activity impairment					<.0001
N	3320	1329	1649	342	
Mean (SD)	**31.6 (23.1)**	**33.8 (22.8)**	**28.6 (23.1)**	**37.5 (22.6)**	
Median	30.0	30.0	20.0	30.0	
HRU					
Ever had LUTS-related surgery, n (%)					.0280
N	3298	1316	1654	328	
No	**3101 (94.0)**	**1252 (95.1)**	**1537 (92.9)**	**312 (95.1)**	
Yes	**197 (6.0)**	**64 (4.9)**	**117 (7.1)**	**16 (4.9)**	
Hospitalisation in the last 12 mo, n (%)					.0067
N	3498	1394	1756	348	

(Continues)

TABLE 4 (Continued)

	Overall	OAB-only	BPH-only	Nocturia-only	*P* value
No	**3359 (96.0)**	**1354 (97.1)**	**1668 (95.0)**	**337 (96.8)**	
Yes	139 (4.0)	40 (2.9)	88 (5.0)	11 (3.2)	
Currently use pads, n (%)					<.0001
N	3479	1387	1738	354	
No	**2784 (80.0)**	**880 (63.4)**	**1647 (94.8)**	**257 (72.6)**	
Yes	**695 (20.0)**	**507 (36.6)**	**91 (5.2)**	**97 (27.4)**	
Number of pads per week					<.0001
N	3441	1362	1729	350	
Mean (SD)	**2.7 (7.3)**	**5.2 (9.8)**	**0.6 (3.0)**	**3.5 (7.7)**	
Number of physician visits in the last 3 mo					.1228
N	2764	1065	1406	293	
Mean (SD)	2.4 (1.8)	2.4 (1.7)	2.4 (1.8)	2.6 (2.2)	
Median	2.0	2.0	2.0	2.0	

Note: The number of observations may vary between the variables because of missing observations. Bold values indicate statistically significant differences between groups ($P < 0.05$).

Abbreviations: BPH, benign prostatic hyperplasia; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; HRQoL, health-related quality of life; HRU, health resource utilisation; LUTS, lower urinary tract symptoms; OAB-q, overactive bladder questionnaire; VAS, visual analogue scale.

group with those of the OAB-only and the BPH-only groups, a multivariate regression analysis was conducted.

3 | RESULTS

As shown in Table 3, a total of 3552 patients were eligible for the designed analysis, with 2876 patients coming from the four European countries plus 676 patients from the United States. Three hundred and fifty-eight nocturia-only patients were identified, accounting for 10.1% of the total sample analysed. The nocturia-only group had a mean body mass index of 27.3 and mean age of 61.2 years; 60.6% were women and 87.2% were Caucasian. In terms of comorbidities, nocturia-only patients were mainly diagnosed with depression and/or other psychiatric problems (28.5%), hypertension (38.3%) and diabetes (22.1%). The groups seem to be rather heterogeneous.

Therefore, Table 4 shows the bivariate analysis results on HRQoL, productivity and HRU. Statistically significant differences were observed for a number of outcomes including EQ-5D VAS, OAB-q (symptom severity, total HRQoL score), likelihood of employment, overall work impairment, activity impairment, hospitalisations, likelihood of surgery, likelihood of use and number of pads.

Results from the multivariate regression analysis are presented in Table 5. The analysis showed that most of the differences in the results were identified when comparing nocturia-only patients with the BPH-only group.

Significant differences ($P < .001$) were observed in most HRQoL instruments, showing that the nocturia-only group had significantly worse quality of life as a result of their condition than that of the BPH-only patients. The productivity measurement (WPAI) presented more mixed results across its domains. Nocturia-only patients were less likely to be employed, and more impaired at work. There was also a significant difference observed for activity impairment. For HRU, the BPH-only group visited physicians less frequently and used fewer pads than the nocturia group.

For OAB-only, outcomes with a statistically significant difference were observed in EQ-5D VAS and OAB-q total score, indicating that nocturia-only patients were likely to suffer from a lower HRQoL compared with the OAB-only group.

4 | DISCUSSION

The results showed that nocturia-only patients experienced a significantly lower HRQoL compared with OAB-only patients. Such differences were not observed regarding productivity score and HRU.

Stronger results were derived from the comparison between nocturia-only group and BPH-only group. Overall, the HRQoL in patients with nocturia was worse, and some aspects of the lower productivity score and more frequent physician visits also indicated that nocturia caused a higher burden to patients' daily life. It was more likely for BPH patients to receive surgery, which might explain the more pads used.

Literature has pointed to a delay in the proper diagnosis, or even misdiagnosis and poor management of the nocturia condition.[1,5,19] Kobelt's study[20] confirms that nocturia significantly reduces the general quality of life and work productivity for those who conduct active professional activities. This important aspect has recently been confirmed in a huge, comprehensive (90 000 plus) workplace survey in the UK, Australia and five Asian countries.[21]

Sleep disturbance as a result of waking up to void during night is another burden to the nocturia patients.[7,8,22] Similarly, the expert

TABLE 5 Multivariate regression results comparing OAB-only and BPH-only groups to the nocturia-only group on HRQoL, productivity and HRU*

	OAB-only		BPH-only		
	Coef/OR	*P*-value	Coef/OR	*P*-value	Adjusted R^2
HRQoL					
EQ-5D-5L state valuation[a]	0.009	.371	**0.039**	**.001**	0.206
EQ-5D VAS[a]	**2.48**	**.006**	**5.36**		0.180
OAB-q symptom severity[a]	−1.9	.108	**NA**		0.095
OAB-q Total HRQoL Score[a]	**−2.7**	**.013**	**NA**		0.074
Productivity					
WPAI: %Employed[b]	1.46	.053	**1.8**	**.011**	0.365
WPAI: % work time missed[a]	1.51	.259	3.2	.066	0.029
WPAI: % impairment while working[a]	−2.1	.365	**−6.53**	**.031**	0.059
WPAI: % overall work impairment[a]	−1.55	.551	−5.66	.096	0.051
WPAI: % activity impairment[a]	−1.96	.182	**−8.71**	**<.001**	0.071
HRU					
Ever had LUTS-related surgery?[b]	1.24	.516	0.97	.921	0.085
Hospitalisation in the last 12 mo?[b]	1.26	.584	1.46	.39	0.050
Currently use pads due to urine leakage[b]	1.21	.222	**0.39**	**<.001**	0.233
Number of pads per week[a]	0.09	.267	0	.979	0.037
Number of physician visits in the last 3 mo[c]	−0.05	.24	**−0.16**	**.002**	0.017

Note: The number of observations may vary between the variables because of missing observations.
Abbreviations: BPH, benign prostatic hyperplasia; EQ-5D-5L, EuroQoL 5 Dimension 5 Level; HRQoL, health-related quality of life; HRU, health resource utilisation; LUTS, lower urinary tract symptoms; OAB-q, overactive bladder questionnaire; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment.
[a]Coefficient provided from a linear regression
[b]Odds ratio provided from a logistic regression
[c]Coefficient provided from a Poisson regression
*$P < .05$ are highlighted in bold.

panel led by Chapple and his co-authors recognises nocturia as the most burdensome LUTS and recommend that new studies on the relation between nocturia, quality of sleep and quality of life measurement should be incorporated when investigating new treatments for LUTS/BPH.[6] What's more, several recent studies reveal that the negative impact of nocturia on HRQoL associated with an increasing number of voids (>2 voids per night).[23]

This study has therefore provided further evidence of the impact of this condition. As nocturia can be underdiagnosed[1]—and therefore can go unrecognised—there is a clear need for better diagnosis, as well as a targeted treatment to reduce the bothersome aspects of nocturia.[24,25]

The strengths of this study include the richness of patient data, the pragmatic selection of a targeted population based on real-world treatment practice and the variety of outcomes assessed. The large sample size allowed us to focus exclusively on patients with a single-diagnosis (n = 3552) so the results would potentially not be confounded by a combination effect of other LUTS conditions. But this kind of real-world data also comes with some potential weaknesses. While it should be highlighted that all patients included in the survey had a physician-confirmed diagnosis, the authors do rely on the accuracy of the physician diagnosis and recording. To support the physician in correctly diagnosing the patient, we included several questions relating to symptoms and ways of arriving at the diagnosis. It is of course still possible that patients with de facto nocturia condition might have been diagnosed with a combination of nocturia and other LUTS (and thus excluded), or even incorrectly diagnosed as OAB and/or BPH patients. Diagnosis bias may also go in the other direction. The fact that 27% of nocturia-only patients wear pads may indicate this. However, we would then anticipate that the differences between the groups might in fact be greater than stated in this analysis.

One key aspect in HRQoL research is of course whether these differences are clinically meaningful or not. While the different instruments clearly point to a large impact on their daily life, the average differences between the different groups are most likely not clinically meaningful.

To conclude, nocturia patients in major European countries and the US experienced statistically significant worse quality of life compared with patients with OAB or BPH. Taking all factors into consideration, nocturia can severely impact patients' quality of life. Thus,

appropriate practices need to be established for the recognition and treatment of patients with nocturia.

ACKNOWLEDGEMENTS

This paper specifically refers to the analytical methodology used to assess the quality of life and HRU in patients with nocturia, OAB and BPH. The patient-reported data were extracted from the LUTS Disease Specific Programme™ developed by Adelphi Real World.

CONFLICT OF INTEREST

FA is employed by Ferring Pharmaceuticals A/S, and VYZ is a former employee of Ferring. GM, JP and PA are employees of Adelphi Group Ltd. Funding to Adelphi for this study came from Ferring Pharmaceuticals A/S.

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