The Measurement of Nocturia and Its Impact on Quality of Sleep and Quality of Life in LUTS/BPH

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Abstract

Nocturia is one of the most bothersome complaints in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). This is probably due to the fact that nocturia interferes with the quality of sleep which may have a significant negative impact on how the patient feels the next day in terms of energy level, concentration and mood and ultimately his overall quality of life (QoL). Disturbed sleep due to nocturia may even lead to increased long-term morbidity and mortality. More attention should therefore be paid to nocturia in clinical practice, in the initial evaluation of the LUTS/BPH patient, and in clinical research, in the evaluation of the benefits of (new) LUTS/BPH treatments. In LUTS/BPH a number of methods are available to assess the frequency of nocturnal voids and its impact on QoL, however, none were specifically designed or developed for this purpose. In addition, there are no methods evaluating the impact of nocturia on quality of sleep. Clearly there is a lack of specific, sensitive and validated methods assessing the impact of nocturia on quality of sleep and QoL. The recently developed validated Nocturia Quality of Life (N-QOL) questionnaire may be a useful tool for this. It appears that it is not only the frequency of nocturnal voids but also its timing that impacts on the bothersomeness of nocturia. The hours of undisturbed sleep (HUS), defined as the time from falling asleep to first wakening to void, may provide a useful method to assess the impact of nocturia on quality of sleep. Data from objective sleep assessment tools, such as actigraphy, combined with data from subjective sleep diaries/logs may accurately estimate the HUS.

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1. Introduction

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) is a common condition over the age of 40 years. In its treatment urologists have focussed for many years mainly on improving flow rate and voiding (“obstructive”) symptoms (e.g. slow stream, intermittency, hesitancy, straining, terminal dribble) and preventing the progression to acute urinary retention (AUR). This could be achieved by removing the enlarged prostate by prostatic surgery (e.g. transurethral resection of the prostate (TURP)). However, in some cases, TURP did not result in complete relief of symptoms. It appeared that TURP relieved voiding symptoms more rapidly and/or to a larger extent than storage (“irritative”) symptoms (e.g. increased daytime frequency, nocturia, urgency) [1–4]. In addition, it was observed that failure of TURP was often due to persistence and/or deterioration of storage symptoms [2,4]. When looking at the urinary symptoms experienced by LUTS/BPH patients, voiding symptoms are most prevalent. However, storage symptoms are generally considered as most bothersome by the patient as they may interfere with daily life activities and negatively affect quality of life (QoL) [5]. It has been recognised that nocturia, i.e. the complaint that the individual has to wake at night one or more times to void [6], with each void preceded and followed by sleep [7], is one of the most bothersome storage symptoms in patients with LUTS/BPH because it negatively impacts on the quality of sleep and QoL [8]. As patients with LUTS/BPH seek medical advice because they are bothered by their symptoms, more attention should be paid in clinical practice and clinical research to storage symptoms and in particular to nocturia. The means by which nocturia and its impact on quality of sleep and QoL are measured is essential in this respect. This paper reports on data presented during a presentation that was held during a satellite symposium on New Developments in Prostate Cancer and Prostate Diseases, held from June 24–27, 2005 in Paris, France that specifically focussed on nocturia and its impact on quality of sleep and QoL and the instruments to measure these items within the field of LUTS/BPH.

2. The impact of nocturia on quality of sleep and QoL

Nocturia is one of the most bothersome symptoms in patients with LUTS/BPH, not only for the patient but also for his partner [9]. This is probably due to the fact that nocturia is the major cause of disturbed sleep. In a Dutch epidemiological study among elderly men aged 50–93 years, nocturia was the most common cause of sleep disturbance (Fig. 1) [8,10]. Increased severity of nocturia leads to increased sleep disturbance such as frequent awakenings and poor sleep (Fig. 2) [11]. Furthermore, not only does increased frequency of nocturnal voids negatively impact on the quality of sleep, it also results in decreased perceived daytime vitality/energy and general feeling of well-being (Fig. 2) [11]. This is probably due to the fact that disturbed sleep with reduced daytime energy interferes with concentration, mood and performance of daily life activities [8,12]. For example, the sleep interruption associated with nocturia may induce cognitive impairment [8,13] and may lead to impaired productivity at work [8,14]. Nocturics also have an increased use of healthcare services [15]. This indicates that nocturia not only imposes a burden on patients and their partners, but that its costs for society may also be considerable [8]. Nocturia and/or disturbed sleep not only decrease the QoL of patients with LUTS/BPH, they can also have more serious consequences. Excessive fatigue and reduced concentration due to lack of sleep is also believed to be a major risk for road traffic accidents [8,16] and occupational accidents [8,17]. Approximately 20% of all motor vehicle accidents are due to fatigue or falling asleep [18,19]. There are also indications that lack of sleep (due to nocturia) may increase the risk of morbidity (e.g. depression, cardiovascular disease and diabetes) and perhaps even mortality [8,20–23]. As nocturia has a significant negative impact on the quality of sleep and the QoL of patients with LUTS/BPH, its measurement should be part of the
initial evaluation of the patient with LUTS/BPH and in the assessment of the benefits of (new) LUTS/BPH treatment. However, the question then rises on how to measure nocturia and its impact on quality of sleep and QoL.

3. How has nocturia and its impact on quality of sleep and QoL been measured in LUTS/BPH clinical research?

3.1. Clinical trials on nocturia in LUTS/BPH

When looking at clinical trials in the field of LUTS/BPH it should first be noted that little research has been devoted to nocturia and its impact on quality of sleep and QoL. Most of the studies performed were also not specifically designed or powered to evaluate nocturia. The Veterans Affairs (VA) Cooperative trial, including 1,040 LUTS/BPH patients with at least 1 nocturnal void, showed that 1 year treatment with an $\alpha_1$-adrenoceptor (AR) antagonist or combination therapy of an $\alpha_1$-AR antagonist and the 5α-reductase inhibitor finasteride reduced the frequency of nocturnal voids to a statistically significantly greater extent than either placebo or finasteride [24]. In a pooled analysis of 3 double-blind trials in LUTS/BPH patients with $\geq$2 nocturnal voids the 5α-reductase inhibitor dutasteride improved the frequency of nocturnal voids statistically significantly more than placebo [25] but to a comparable extent as finasteride in the VA Cooperative study [24]. Two Japanese studies showed that both medical therapy (mainly consisting of $\alpha_1$-AR antagonists) and surgery reduced the frequency of nocturnal voids in LUTS/BPH patients. Surgery reduced the frequency of nocturnal voids to a slightly larger extent, however, patients treated with surgery also had a higher frequency of nocturnal voids at baseline [26,27]. Other clinical studies have also evaluated the impact of medical treatment on the frequency of single symptoms of LUTS/BPH including nocturia [28–31]. However, most of these studies were not primarily designed and powered to assess the impact of LUTS/BPH treatment on nocturia and therefore some of them probably failed to show statistically significant improvements in the frequency of nocturnal voids vs. placebo.

3.2. Measurement of the frequency of nocturnal voids

The trials discussed above measured the quantitative domain of nocturia, i.e. the frequency of getting up at night to void. This is often assessed by means of the nocturia question included in the International Prostate Symptom Score (I-PSS) [32] (Fig. 3). For this question the patient has to indicate how many times over the past month he most typically had to get up to urinate from the time he went to bed until the time he got up in the morning. This can range from none (score 0) to 5 or more times (score 5) per night. However, the I-PSS questionnaire was neither developed nor evaluated for the measurement of nocturia and may be subject to recall bias. Other questionnaires are available that measure frequency of symptoms of LUTS/BPH and that include a question on the frequency of nocturnal
voids, e.g. the Boyarsky symptom score [33], the Madsen-Iversen Symptom Score [34], and the ICsmaN questionnaire [35]. However, these suffer from the same drawbacks as the I-PSS. Although not often used in clinical trials, a voiding diary, on which a patient has to indicate how many times and at what times he voided at night, may also be used to measure the frequency of nocturnal voids (Fig. 3). However, this may also be prone to recall bias.

3.3. Measurement of the bothersomeness of nocturia

Although no clinical trials in the field of LUTS/BPH have evaluated the impact of nocturia on QoL, it is recognised that nocturia is a very bothersome symptom. There are a number of methods that could potentially be used to measure the qualitative domain of nocturia, i.e. its bothersomeness. These include generic QoL questionnaires and disease specific QoL questionnaires (Fig. 3). One of the main generic instruments for measuring QoL is the Short Form 36 (SF-36) [36,37]. This measures the overall physical, psychological and social function by means of 36 questions in 8 domains (physical functioning, role-physical, bodily pain, general health perceptions, vitality, social functioning, role-emotional and mental health). The SF-36 questionnaire has for instance been used in a Swedish survey to measure the effect of nocturia on vitality/energy and social functioning [14]. Nevertheless, this general non-disease specific questionnaire may be too crude and not sensitive enough to measure the impact of nocturia due to LUTS/BPH on QoL or for instance LUTS/BPH treatment induced changes in nocturia and its impact on QoL.

A number of questionnaires are available that evaluate the impact of LUTS/BPH on every day QoL. These include among others the BPH Impact Index [38], the International Continence Society Quality of Life questionnaire (ICSOl) [39], the BPH Health Related Quality of Life (BPH-HRQOL) questionnaire [40] and the BPH specific Interference with Activities Scale [41]. However, these questionnaires do not look specifically at the impact of nocturia but rather at the impact of urinary symptoms in general on QoL and activities of daily living. One question on the impact of LUTS/BPH on QoL has been included in the I-PSS: ‘if you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?’ The score ranges from delighted (score 0) to terrible (score 6) [32]. However, this single question also measures the effect of the present urinary condition on QoL and is not specific for nocturia. A questionnaire that assesses the impact of several urinary symptoms on QoL is the Symptom Problem Index (SPI) [38]. It contains 7 questions which are aimed at the degree to which the present symptoms are a problem for the patient. This questionnaire also includes an item on nocturia asking the patient: ‘over the past month, how much has getting up at night to urinate been a problem for you?’ with a score ranging from no problem (score 0) to big problem (score 4). However, this single question was not designed nor evaluated for measuring the impact of nocturia on QoL. The Danish Prostatic Symptom Score (DAN-PSS-1) attempts to both quantify and qualify symptoms by combining a symptom score and a bother score [42,43]. The severity of each symptom and the degree of bother is scored from 0 to 3. A weighted score is then obtained by multiplying the symptom score and bother score. Questions on the frequency and bothersomeness of nocturia are included in this questionnaire but there is currently little data with this questionnaire and the single questions on nocturia were not designed nor evaluated for measuring the impact of nocturia on QoL.

3.4. Measurement of the impact of nocturia on quality of sleep

Within LUTS/BPH no questionnaire specifically evaluates the impact of nocturia on quality of sleep. In sleep research the impact of nocturia on quality of sleep has mainly been investigated by means of self-constructed, non-validated questionnaires [11, 44,45].

It seems that although there are a number of methods available in the field of LUTS/BPH that measure the frequency of nocturnal voids and its bothersomeness, most appear to be not sensitive enough nor are specifically designed and validated. In addition, there are no validated methods that
assess the impact of nocturia on quality of sleep. However, recently there have been a number of interesting developments in these areas, which will be discussed in the following paragraph.

4. Recent developments in the measurement of nocturia and its impact on quality of sleep and QoL in LUTS/BPH

4.1. Questionnaires on nocturia and its impact on quality of sleep and QoL

Recently 2 questionnaires were constructed that focus on the qualitative domain of nocturia, i.e. its bothersomeness (Fig. 3). Abraham et al. [46] have developed a validated questionnaire that specifically measures the effect of nocturia on quality of sleep and QoL: the Nocturia Specific Quality of Life questionnaire (N-QOL; Table 1). This is a 13-item questionnaire which consists of 3 domains/sub-scales: a sleep/energy domain consisting of 7 questions (score range 0–28), a bother/concern domain consisting of 5 questions (score range 0–20) and one global QoL question (score range 0–4). It deals with daytime energy, worry, productivity, sleep and vitality. This self-administered questionnaire takes about 5 minutes to complete and has been proven to be internally consistent and reproducible. It has also been shown to correlate with the energy/vitality domains of the SF-36 [32] and with the sleep quality domain of the Pittsburgh Sleep Quality Index [47]. The N-QOL has become one of the modules of the International Consultation on Incontinence Questionnaire-Nocturia (ICIQ-N) that is currently under development [48]. The other 3 modules of the ICIQ-N consist of a nocturia domain (2 questions on the frequency and bothersomeness of nocturia), a sexual domain (6 questions) and a general health domain (6 questions from the SF-12 [49]).

4.2. The Hours of Undisturbed Sleep (HUS)

A potential new method to measure (the impact of nocturia on) the quality of sleep are the Hours of Undisturbed Sleep (HUS). It has been shown that deep, slow wave, restorative sleep occurs during the first hours of the night, while in the second part of the night, the lighter (less restorative) sleep predominates. It is mainly a decrease in deep sleep that contributes to daytime fatigue. Waking up in the first 3–4 hours of the night during deep, slow wave, restorative sleep is therefore more likely to leave a person groggy and tired during the following day than waking up later at night [50,51]. It is therefore not only the frequency of nocturnal voids that impacts on quality of sleep and QoL but also the timing of wakening up to void (Fig. 3). Based on this, the concept of HUS was developed as a proxy for quality of sleep. HUS is defined as the time from falling asleep to first wakening to void and should last at least 3–4 hours [52]. This concept was recently used in a proof of concept, pilot study evaluating the effect of tamsulosin oral controlled absorption system (OCAS®) 0.4 mg once daily on nocturia, quality of sleep and QoL in LUTS/BPH patients with nocturia and disturbed sleep [52]. In this study the HUS was measured by means of a diary, the frequency of nocturnal voids was assessed by means of the I-PSS nocturia question [32] and by means of a diary and QoL was assessed by means of the I-PSS QoL question [32]. It was shown that the decrease in the frequency of nocturnal voids correlated with an increase in HUS and QoL thus suggesting that there is a relationship between the frequency of nocturnal voids, HUS and QoL [52]. There was an increase in HUS with tamsulosin OCAS® 0.4 mg once daily of 81 minutes vs. baseline. However, this was not statistically significant vs. placebo, which was probably due to the fact that this was a pilot study with a small number of patients. In addition, it was discussed by the authors that more appropriate measuring tools that more accurately assess the actual sleep patterns of the patients may have yielded better results since self-administered diaries on night-time behaviour may contain inaccuracies [52]. Sleep logs/diaries, may be subject to recall bias and may overestimate sleep onset latency and underestimate sleep time [53,54]. Therefore it is generally recommended that subjective assessment of sleep should be complemented by an objective measurement. Polysomnography (PSG) is the gold standard objective sleep assessment method. It is a diagnostic test during which a number of physiologic variables are measured and recorded during sleep, such as: brain electrical activity, eye and jaw muscle movement, leg muscle movement, air flow, respiratory effort, electrocardiogram and oxygen saturation. However, it is an expensive procedure that many individuals find intrusive and burdensome. In addition, it can only be performed in sleep laboratory and is therefore not suitable for clinical practice.

Actigraphy is an alternative sleep assessment method that measures body movements, by means of a wrist-worn activity meter. It is based on the principle that there is reduced movement during sleep and increased movement when the patient gets up for example to void. The time, the number and frequency of awakenings/nocturia episodes can then be assessed. Advantages of actigraphy include its
ease of use, its low cost, non-invasive nature and automated sleep scoring and data storage which is also possible in the ambulatory setting for a longer-time period. Comparison of actigraphy with PSG has yielded agreement rates of about 90% in normal people without sleep disorders [55]. In patients with sleep disorders actigraphy slightly tended to overestimate sleep efficiency and total sleep time in comparison to PSG [56]. In studies comparing data from actigraphy, a sleep diary and PSG, actigraphy data were more accurate than sleep diary data when compared to PSG [54]. However, when data from actigraphy and a sleep diary/log were combined total sleep time and sleep efficiency did not significantly differ from PSG [57]. The authors recommend the combined use of actigraphy with sleep logs in patients with disturbed sleep [57]. The American Academy of Sleep Medicine considers actigraphy appropriate for the assessment of treatment effects on sleep. In addition, it was concluded that in sleep-disordered patients the combined use of actigraphy and subjective questionnaires has advantages [56].

<table>
<thead>
<tr>
<th>Table 1 – The Nocturia Specific Quality of Life Questionnaire (N-QOL) [46]</th>
</tr>
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<tbody>
<tr>
<td>OVER THE PAST 2 WEEKS HAVING TO GET UP TO URINATE ......</td>
</tr>
<tr>
<td>1. Has made it difficult for me to concentrate the next day</td>
</tr>
<tr>
<td>2. Has made me feel generally low in energy the next day</td>
</tr>
<tr>
<td>3. Has required me to nap during the day</td>
</tr>
<tr>
<td>4. Has made me less productive the next day</td>
</tr>
<tr>
<td>5. Has caused me to participate less in activities I enjoy</td>
</tr>
<tr>
<td>6. Has caused me to be careful about when or how much I drink</td>
</tr>
<tr>
<td>7. Has made it difficult for me to get enough sleep at night</td>
</tr>
</tbody>
</table>

OVER THE PAST 2 WEEKS, I HAVE BEEN......

| 8. Concerned that I am disturbing others in the house because of having to get up at night to urinate | □ Extremely □ Quite a bit □ Moderately □ A little bit □ Not at all |
| 9. Preoccupied about having to get up at night to urinate | □ All the time □ Most of the time □ Some of the time □ Rarely □ Never |
| 10. Worried that this condition will get worse in the future | □ Extremely □ Quite a bit □ Moderately □ A little bit □ Not at all |
| 11. Worried that there is no effective treatment for this condition (having to get up at night to urinate) | □ Extremely □ Quite a bit □ Moderately □ A little bit □ Not at all |

12. Overall, how bothersome has getting up at night to urinate been during the past 2 weeks?
 □ Not at all
 □ A little bit
 □ Moderately
 □ Quite a bit
 □ Extremely

13. Overall, I would rate my quality of life to be
 □ Very good
 □ Good
 □ Fair
 □ Poor
 □ Very poor

The REMview is a relatively new method that includes an eyelid electrode to detect eye movements, a head cap or headband housing a sensor to detect head movements, and a small recording device. It assesses wakefulness, rapid eye movement (REM) sleep and non-REM sleep [58]. However, REMView requires additional testing to show that this device outperforms other available sleep assessment methods [58].

5. Conclusions

It is increasingly recognised that nocturia is one of the most bothersome symptoms of LUTS/BPH because it negatively affects sleep and QoL of both the patient and his partner. Unfortunately, the impact of nocturia on quality of sleep and QoL is not yet a key element in the evaluation of patients with LUTS/BPH and limited attention is given to measuring the frequency of nocturnal voids, its impact on quality of sleep and QoL in clinical urological research. Indeed, clearly an unmet need exists for better evaluation of nocturia and its impact on quality of sleep and QoL. The recently developed methods for measuring nocturia and its impact on quality of sleep and QoL, i.e. the N-QOL, the ICIQ-N and HUS may become useful tools in this respect. The information obtained by these methods will provide more insight into the extent to which a LUTS/BPH patient suffers from nocturia, the disturbing effect on his sleep and its bothersomeness in daily life, and the potential of LUTS/BPH treatment to reduce the patient’s nocturia and ultimately to improve his quality of sleep and QoL.

It appears that it is not only the frequency of nocturnal voids that determines the impact on QoL, but that also the timing of waking up to void is important. The HUS may therefore provide a useful method for measuring the impact of nocturia on quality of sleep but it needs to be established how an increase in the HUS translates into improved daytime energy and QoL of the patient. Data from advanced sleep assessment tools, such as actigraphy, may complement subjective sleep data obtained by sleep diaries/logs and provide an accurate measurement of the HUS.

References


[17] Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Work organization and unin-


