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Nocturia: The circadian voiding disorder

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Nocturia is a prevalent condition of waking to void during the night. The concept of nocturia has evolved from being a symptomatic aspect of disease associated with the prostate or bladder to a form of lower urinary tract disorder. However, recent advances in circadian biology and sleep science suggest that it might be important to consider nocturia as a form of circadian dysfunction. In the current review, nocturia is reexamined with an introduction to sleep disorders and recent findings in circadian biology in an attempt to highlight the importance of rediscovering nocturia as a problem of chronobiology.

Keywords: Circadian clocks; Circadian rhythm; Lower urinary tract symptoms; Nocturia; Sleep wake disorders

INTRODUCTION

Nocturia is a prevalent condition of waking to void during the night that is relatively recalcitrant to treatment aimed at lower urinary tract symptoms, either surgical or pharmacologic. The incidence of nocturia increases with age. So prevalent is nocturia in the aging population that most patients commonly do not consider it a symptom to be treated but rather a natural progression to be accepted with aging. This highlights the insidious nature of nocturia. Should the condition remain generally benign and not warranting of particular attention this would have not mattered. However, studies have shown that interrupted sleep itself is potentially harmful and debilitating, severely diminishing quality of life, having a significant association with mental disorders, and increasing the risk of hypertension, diabetes, and malignancies [1-4].

Despite these attributes, nocturia has traditionally been considered as part of the spectrum of lower urinary tract symptoms, if not a symptom of the prostate [5]. As such, research into evaluation and treatment of nocturia is often mixed with that for lower urinary tract symptoms [6]. This approach of bundling heterogeneous symptoms has hampered investigation of nocturia, and it was only recently that observing nocturia as a symptom in itself has yielded palpable results [7].

This review focuses on the emergent etiology of nocturia and discerns treatment effects solely based on evaluation centered on nocturia itself, while providing contrasts in the dangers of mixing symptoms of lower urinary tract symptoms with the symptoms of nocturia.

PREVALENCE, EPIDEMIOLOGY, AND DEFINITIONS

Nocturia has commonly been considered a disease of the aging male [8]. However, epidemiologic reports persistently suggest otherwise. The European Prospective Investigation into Cancer and Nutrition study, performed across five countries including 19,165 participants, reported nocturia

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as the most prevalent lower urinary tract symptoms in both men (48.6%) and women (54.5%) when defined as more than 1 void per night [9]. When considering nocturia with the commonly used definition pertaining to "clinically meaningful" of more than 2 voids per night, the prevalence remained 20.9% for men and 24.0% for women. For nocturia defined as more than 2 voids per night, prevalence was higher in women than in men across all age brackets. Nocturia was also not insignificant in younger patients less than 40 years of age (12.9% for men and 16.9% for women for clinically bothersome nocturia), presenting a picture of a widely prevalent symptom across all subgroups of age and sex.

A recent meta-analysis that collated data from 1990 to 2009 from 43 articles reported that 28.3% to 61.5% of women void more than 2 times per night and 29% to 59.3% of men do [10]. Although the collated data presented much variance between reports, the overall trend showed that both men and women were significantly affected at comparable rates. Younger patients also reported prevalences of 4.4% to 18% for younger women and 2% to 16.6% for younger men. Thus, multiple sources concur that younger patients also have rates that require attention.

The significance of nocturia in younger patients is highlighted by the fact that these patients are in an active working age bracket and suffer significant bother. A recent Finnish study enrolling 3,474 subjects (from a target of 6,000 sent by mail), and designed to focus on nocturia, investigated bother score associated with nocturia frequency [11]. Despite utilizing the Danish Prostatic Symptom Score (DAN-PSS) and the American Urological Association Symptom Index (AUA-SI), the investigation itself was focused on identifying the association between nocturia and quality of life, rather than lower urinary tract symptoms in general. The results were noticeable in that younger male patients (aged less than 40 years) showed a significantly pronounced decrease in quality of life score when nocturia episodes increased to 2 voids per night, whereas such a significant dip in score is generally noticeable for more than 3 voids or more per night. While increasing bother associated with increasing nocturia episodes is intuitive, bother in the younger age group shows greater burden on daytime activity, an often underappreciated facet of the burden of nocturia in the general population.

In 2002, the International Continence Society defined nocturia as waking up at night from sleep to void [12]. There are a few problems with this definition. Although defining nocturia as once per night highlights the importance of providing a heightened level of surveillance to a generally underestimated symptom, as most bother-related articles have shown, significant nocturia increases only above 2 voids per night. Although it seems intuitive that awakening more is additive to bother, this concept generally evades addressing the underlying mechanisms behind how and to what extent this increase in sleep interruption affects the patient. It was not until recently that studies in nocturia began to recommend evaluation of hours of uninterrupted sleep as a primary factor in reporting results of studies [7]. Erstwhile, outside of urology, the investigation of sleep and sleep-related disorders progressed without properly addressing nocturia, despite being both so prevalent in the population and being obviously more obtuse in its interruption of sleep, as the patient is required to fully become conscious to void, in comparison to its more subtle but more well investigated comorbidities that may only produce effects of light sleep or intense dreaming bouts without awakening [13-15].

Another important point to note is that "night" within the definition, and the inherent etymological origin in the word "nocturia," is limiting in scope. Some patients experience different sleep schedules, pertaining to different day-night cycles, in which the extended duration of their primary sleep does not necessarily occur during the night. Maintaining this definition limits the concepts and problems that research into evaluation and treatment of nocturia must address. This is an important problem that is touched upon later.

THE SCIENCE OF SLEEP

In 1980 Borbely and Achermann [16] proposed the two-process model of sleep homeostasis. The model describes a homeostatic process dependent on the sleep-wake cycle, which increases the burden of sleep during wake and relieves the burden during sleep (Process S), and an independent process controlled by the circadian pacemaker (Process C). The decrease of sleep burden in Process S during sleep triggers awakening, while conversely increasing sleep burden triggers sleep. Physiologically, Process S is best represented in nonrapid eye movement (NREM) sleep electroencephalography slow wave activity as theta activity. In this model, Process C functions independently and additively to gain or decrease Process S and is physiologically represented in core body temperature and melatonin rhythms. Animals injured in the circadian pacemaker center of the suprachiasmatic nucleus maintain sleep homeostasis, despite disrupted circadian rhythm.

The importance of this model is in its ability to explain

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the phenomenon of internal desynchronization between sleep-wake homeostasis and circadian body temperature cycles, as evidenced by the presence of circadian oscillations during prolonged sleep deprivation (3 days), or sleep fragmentation during continuous bedrest, or with sleep duration in shift workers. Under these examples of sleep disruption, Processes S and C interact to cause a dramatic increase or resistance to sleepiness. When a person remains awake for a long time (high sleep pressure; Process S) and also happens to be awake at night, when the circadian system is strongly promoting sleep, a strong bout of sleepiness much worse than that predicted by simply adding their effects together occurs. Concerning people with 24-hour shifts, this makes it particularly dangerous to be working between 3:00 AM and 6:00 AM when circadian rhythms of sleepiness reach their peak, coupled with a built-up sleep pressure due to the extended time awake.

The problem of sleep interruption, what may happen for multiple episodes of nocturia, is not as simple. Several complex mechanisms are involved in predicting the effects of sleep following sleep interruption during the previous phase of sleep. The diagnosis and pathophysiology may or may not have been inherently due to nocturia and bladder sensation, or merely an outcome of difficulty in maintaining sleep. Sleep maintenance insomnia, which is more frequent in older adults, has been reported to be as prevalent as 23% of the population [17]. Almost half of these patients (43%) reported having difficulty resuming sleep once awake, and these tendencies were strongly associated with impairment of daytime functioning. Investigation of sleep interruption in rats suggested that sleep fragmentation resulted in a significant reduction in REM sleep time and a greater increase in homeostatic sleep pressure than in NREM sleep [18].

Unfortunately, the interpretation of more complex scenarios is not only beyond the scope of the current review, but in relation to nocturia, beyond current scientific understanding as of yet. People react to sleep deprivation differently. Some are more resilient, whereas others are susceptible to daytime sleepiness [13,19]. Furthermore, recent discoveries suggest that the previously considered independent Processes of S and C are now mutually influencing, forgoing the previously stated tenets that these processes neatly fall into simple mathematical formulae [20-22]. The study of circadian rhythms only becomes more complex.

THE MOLECULAR BASIS OF THE CIRCADIAN CLOCK

At the beginning of the new millennium, sleep and circadian researchers postulated that circadian rhythmicity could be described as a negative feedback loop involving a core clock protein. Transcription of these core clock proteins would affect themselves as well as their myriad targets conveying circadian rhythmicity. The circadian proteins circadian locomotor output cycles kaput (Clock) and brain and muscle Arnt-like protein-1 (Bmal1) heterodimerize to interact with the promoters of clock-controlled genes, among which the proteins period (Per) and cryptochrome-like protein (Cry) translocate to the nucleus to inhibit the activity of Clock and Bmal1 (Fig. 1) [23,24].

Whereas at the cellular level, a cell can express its own independent clock, on the organismal level, this activity is coordinated through the role of a central clock that dictates the "time" of the body throughout various

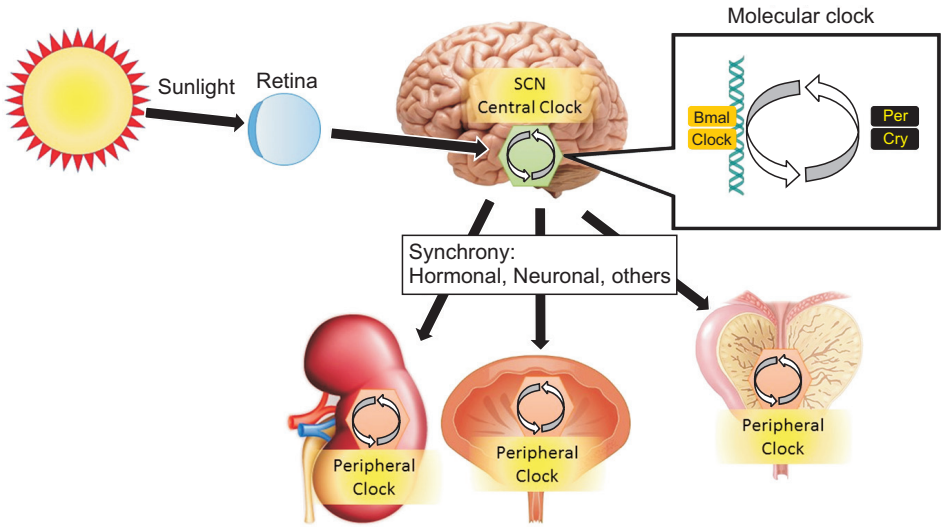

Fig. 1. The circadian process centers around the central clock located in the suprachiasmatic nucleus (SCN), which coordinates with each peripheral molecular clock, through various mechanisms, in synchrony with environmental cues, principally received through light. This synchrony with internal clocks and with the external environment maintains corrections to the molecular cycle which also proceeds through a roughly 24-hour pattern.

peripheral clocks [25]. The primary central clock resides in the suprachiasmatic nucleus of the brain. Light entering through the retina causes signals to pass through the retinal hypothalamic tract affecting and correlating the bodily clock to the environmental day-night cycle. Other physiologic signals, such as feeding cues, also affect the central clock in the suprachiasmatic nucleus.

Although it may be suggested that the central clock maintains complete control over peripheral clocks, dictating behavior in terms of chronobiology, recent evidence suggests that each peripheral clock is independent, responding to central cues and collating these signals with their own internal cues [26]. Most prominent of these circadian peripheral effects are highlighted in association with nutrition. As noted previously, feeding cues are a significant regulator of circadian rhythm. Studies have shown that downstream to the clocks, SIRT-1 and NAD influence the function of the clock, especially in the liver [27,28]. The metabolic examples of circadian influence highlight the role of chronobiology as a method of compartmentalization, not with special cellular function, but through time-related compartmentalization [29].

NOCTURIA, THE CIRCADIAN DISORDER

Despite these advances in circadian research, nocturia research has only recently begun. Although physiologic variation in urine output has been documented for a long time, becoming one of the cornerstones of pharmacologic treatment of nocturia, the association with circadian genes has only recently been uncovered [30]. In vascular smooth muscle, various clock components oscillate and dictate the levels of key components. In Bmal1-knockout mice, endothelial peroxisome proliferator activated receptor γ is significantly reduced [31]. Clock-knockout mice express phenotypes of hypotension, diabetes insipidus, and dysregulated sodium excretion in the kidneys [32]. Per1 regulates endothelin-1 and ENaC, whereas Per1 and Per2-knockout mice lose circadian urine production rhythmicity [33,34].

The bladder has also recently been identified as being heavily influenced by circadian genes. Studies have demonstrated active circadian gene cycling in all levels of bladder tissue [35]. The bladder gap junction protein, connexin 43, was shown to lose circadian rhythmicity of expression in Cry-knockout mice [36].

In lieu of these advances in multiorgan circadian dysfunction, nocturia could be addressed as principally a circadian dysfunction, where the physiologic function of voiding is affected by disrupted circadian rhythms, or vice versa [37]. In a study of mice, Negoro et al. [38] showed the development of the voiding micturition cycle as an emergent phenomena of the organism adapting to the day-night cycle of the environment. Another study recently reported the consequence of dysregulated circadian rhythms, via shift work, which differently affected peripheral organs of the kidney (urine production) and bladder (voiding) [39]. In this study, while the circadian pattern of urine production adapted rather quickly to circadian disruption following shift work, the circadian rhythm of bladder capacity remained recalcitrant to the rapid shifts in day-night rhythms, leading to aggravation of nocturia in shift workers compared to fixed schedule workers.

RE-EXAMINING THE TREATMENT OF NOCTURIA

The central point in the controversy over treating nocturia as a spectrum of lower urinary tract symptoms is the degree of relief provided by ameliorating obstruction, either through alpha-blockers or through surgery of the prostate. Earlier reports seemed to suggest that alpha-blockers, irrespective of which particular agent, generally improved nocturia [6]. Studies with terazosin [40-43], alfuzosin [44-47], tamsulosin [6,40,48,49], and doxazosin [50-52] all enrolled a large number of patients across multiple centers under randomized designs. However, most of these studies used the AUA-SI as the basis for evaluating nocturia. Earlier guidelines that collated these data were sparse in recommending a definitive course of action for nocturia. The older European Association of Urology guideline optionally recommended the use of frequency-volume charts, whereas the AUA guideline failed to mention these [53]. The guidelines further stated that evaluation of the data presented suggested that nocturia frequency was well correlated with reported AUA-SI scores [54].

To do justice, subsequent guidelines quickly advocated the use of frequency-volume charts in patient evaluation, and several reports provided high correlation between symptom score questionnaires and frequency-volume chart records [54-58]. Surgery for the prostate was also uniformly reported to result in an overall improvement in nocturia similar to alpha-blockers. However, Weiss et al. suggested that this might be temporary, and citing a follow-up study, stated that treatment designed to relieve obstruction would not necessarily relieve symptoms of storage as well [59,60].

Recent publications adopt this latter view. In a recent extensive meta-analysis, Cornu et al. [61] stated that little

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evidence supports the effect of α1-blockers on nocturia. The report also precluded the use of surgical intervention for nocturia. Recent guidelines on nocturia stress the importance of completing frequency-volume charts, not only to properly document nocturia but also to analyze and categorize its mechanisms to identify components of nocturnal polyuria and decreased nocturnal bladder capacity as put forth by Weiss et al. [12,62-64].

These recent developments, although finally focusing on nocturia as a disease entity in itself, are not without faults. The meta-analysis by Madersbacher and Cornu [65] excluded not only nonrandomized trials but also publications where the primary focus of investigation was not nocturia. Although this seems intentional, as stated in the statement of introduction to the article, and a follow-up editorial, it also begs the question of whether the previous plethora of reports of the effect of relieving outlet obstruction on nocturia were without merit. More recent combination trials pairing alpha-blockers with anticholinergics, desmopressin, or behavioral therapy still maintain the benefit of alpha-blockers for nocturia with the use of both frequency-volume charts as well as conventional symptom scores [66-68]. A more recent consensus statement by the International Consultations on Urological Diseases (ICUD) reviewed previous randomized controlled trial data on treatment for benign prostatic enlargement and presented a reduction of nocturia episodes of approximately 0.2 to 0.3 voids per night compared with placebo [69]. Considering that the conventional pathophysiology explaining the emergence of secondary storage symptoms following prolonged obstruction is not entirely without merit, future research should attempt to examine alpha-blockers in lieu of current developments in nocturia.

Like the alpha-blockers before, anti-muscarinics have also been criticized for a lack of focus on nocturia-specific tools of evaluation [61,70]. Again, Cornu et al. dismissed most previous evidence on solifenacin [65,71-73], tolterodine [74,75], and other anticholinergics owing to a lack of focus on nocturia, investigation of nocturia as a component of overactive bladder (OAB), or principal use of OAB questionnaires to conduct evaluation of nocturia episodes.

Like alpha-blockers, recent trials for anti-muscarinic therapy have focused on nocturia and have used frequency-volume charts with results comparable to those of older studies [76]. The ICUD consensus also states a reduction of 0.8 voids per night vs. placebo for fesoterodine [69,77].

Recently, the beta-3-agonist mirabegron was introduced to the arsenal of OAB medications. Randomized trials, although aimed at OAB treatment efficacy, did incorporate frequency-volume charts as measurement [78-80]. However, the results varied widely from an improvement of a reduction of 0.2 void per night over placebo to no apparent benefit. As the meta-analysis of Madersbacher and Cornu [65] pointed out, lack of focus on nocturia in previous studies is not only limited to evaluation and outcomes measurement, but also where the focus lies in patient recruitment. Patients with extraneous symptoms that are incidental or unrelated to nocturia may skew the efficacy of outcome. Further investigation enrolling nocturia patients treated with conventional OAB medications but evaluated with principally nocturia-based tools, such as the frequency-volume chart, is required.

Emphasis on the usage of frequency-volume charts has grown in recent years, and accordingly the parametric tools used to analyze nocturia have become a staple of nocturia investigations [64]. Among the various terms defined, the focus has primarily centered on the pathophysiology of nocturnal polyuria. Diurnal variation of arginine vasopressin, or in the pathophysiologic lack thereof, has been documented for some time [81,82]. The circadian fluctuation of vasopressin, and its resulting diurnal variation of urine production, became the basis in treating nocturnal polyuria [83-86]. With the introduction of desmopressin, treatment of nocturia found a method surpassing most conventional lower urinary tract symptom medications in efficacy and improvement of the quality of life [61,87,88].

However, this recent emphasis on treating nocturia with desmopressin is not without retractors. The current ICS definition defines nocturnal urine volume as more than 20% to 33% of total 24-hour urine volume, which is called the nocturnal polyuria index (NPI). The variability of the cutoff allows for the variability in the NPI with increasing age, from 14% in young adults to 33% in the elderly. Alternative definitions also garner a strong following, such as the NUP90, which defines nocturia as nocturnal urine production greater than 90 mL/h [1,64,89]. This definition allows for variability in sleeping hours, which the ICS states should be 8 hours for a valuable evaluation [90]. In a follow-up of the Krimpen study, van Doorn et al. [1] noted that by defining nocturnal polyuria as an NPI of 33%, 78% of the total population was diagnosed as having nocturnal polyuria. In contrast, use of the NUP90 diagnosed 15% of the population with nocturnal polyuria.

Despite unresolved discussion of what defines nocturnal polyuria, current epidemiologic data still state nocturnal polyuria as the most dominant pathophysiologic mechanism causing nocturia [30,61,91-93]. The most significant drawback to the current paradigm of "nocturia by nocturnal polyuria"

is, as van Doorn et al. [1] had hinted, the problem of sleep.

THE FUTURE OF NOCTURIA AND SLEEP

A PubMed search of the terms "nocturia" and "sleep" for clinical trials and observational studies, excluding reviews and cases, returned surprisingly sparse results, only 432 entries. Among the 432 articles, excluding studies in which nocturia was peripheral to other neurologic conditions, sleep disorders, or enuresis in children, only 61 articles were primarily focused on nocturia and sleep in the general population, either treatment or evaluation. Of the 61 articles only 5 studies were observational studies. Two of the 5 articles suggested a tool for assessing sleep quality in nocturia, or the impact of sleep disturbance on nocturia [94,95]. In one of these studies, Bliwise et al. [94] suggested the use of the Pittsburgh Sleep Quality Index, which, interesting enough, the majority of the other 56 nonobservational articles investigating nocturia and sleep with the conventional pharmacologic arsenal of alpha-blockers, antimuscarinics, and desmopressin had incorporated in their trials.

While the current scope of evidence predictably points toward an improvement of sleep quality with pharmacologic interventions, it is interesting to note the lack of investigation beyond the frequency-volume chart and sleep quality questionnaires. Only one study, focused entirely on nocturia and sleep while precluding other conditions such as Parkinson disease or heart conditions, performed polysomnography for nocturia alone in general healthy subjects [96].

In lieu of current developments investigating circadian disorders, sleep disorders, and the changing horizon of nocturia, it may be a good time to begin to focus on nocturia as what it is, voiding during sleep, with an emphasis both on voiding and on sleep.

CONCLUSIONS

The focus in nocturia has shifted considerably from the aspect of prostatic hyperplasia and/or OAB to the current concept stressing abnormal nocturnal urine production. Despite the short time during which these discussions have evolved, the consensus has turned for and against various concepts as rapidly as new pharmacologic agents have been introduced.

Irreverent of the changing landscape in the science of urology, advances in circadian biology have presented a staggering plethora of new information. Considering the obvious association of understanding nocturia as a circadian disorder, as a symptom of voiding at the wrong time, deeper investigation into the fundamental aspects of the pathophysiology of nocturia is necessary.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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