

1 MAIN TEXT

2 Introduction

3 Nocturia is a symptom common to many conditions, however, the causal pathway is multi-
4 factorial and differs between patients (1). Blood pressure changes, cardiac dysfunction, fluid
5 shift into the lower limbs, polyuria, sleep apnoea and insomnia, pharmacotherapy,
6 polypharmacy, mental health disorders, inflammatory processes and bladder dysfunction can all
7 underlie nocturia (2). Multiple causes may co-exist.

8
9 Whilst waking to void once per night in women over 40 years is unlikely to substantially impact
10 health, waking to void twice or more each night has grave consequences, and can be considered
11 “disruptive” or bothersome (2). Nocturia > 2 episodes per night is associated with over four
12 times the risk of developing cardiovascular disease and double the likelihood of early death
13 (Hazard Ratio 1.98, 95% CI 1.09-3.59) (3). Even after adjustment for age, gender, Body Mass
14 Index, diabetes mellitus, smoking, coronary artery disease, renal disease, stroke, hypnotics,
15 diuretic and tranquilizer use, nocturia remains an independent predictor of mortality (3,4). There
16 is a threefold increase in utilisation of health care services in individuals with nocturia.

17
18 Approximately 40% of women older than 40 years report nocturia without other urinary tract
19 symptoms (5). Associations between hormonal depletion and bothersome nocturia have been
20 suggested, with both night sweating and loss of oestrogen known to interrupt sleep and impair
21 wellbeing (1, 6). Nocturia has been reported more often in the presence of hot flushes (38%
22 compared with 32%) (OR 1.49, 95% CI 1.19-1.87) and also in women after a hysterectomy (53%
23 compared with 33%) (OR 1.78, 95% CI 1.08-2.94) (7).

24
25 Little is known about whether hormone status impacts diuresis rate and overall nocturnal urine
26 volume, thereby inducing nocturia, or alternatively reduces the threshold for voiding at night via

sensory or motor changes in the urinary bladder. The aetiology may be mixed but has not been elucidated in women. Greater understanding of post-menopausal factors associated with nocturia will facilitate treatment options for women who wake to void repeatedly at night.

The specific aims of the study were to: i) identify hormonal and lifestyle factors associated with disruptive nocturia (both *self-reported* and *actual nightly voids* recorded on a bladder diary) in women and to ii) understand the relative contribution of altered urine production and bladder storage to number of nightly voids. A further aim was to clarify whether new gender-specific items should be added to the current nocturia causality screening tool, Targeting the Aetiology of Nocturia Guides Outcomes (TANGO) (8).

Materials and Methods

A cross-sectional study was undertaken at three public hospital continence services in Australia. The study was approved by the Human Research Ethics Committee at each participating institution (i. HREC/17/MH/392; ii. 18/G/086 iii.18/WMEAD/272). Because prevalence of night voiding increases after the age of 50 years, women 40 years or older presenting between October 2018 and December 2019 were approached. Nocturia was not an eligibility criteria. Conditions that may be associated with atypical urine production or storage; dementia or cognitive impairment that precluded completing a questionnaire and inability to communicate in English, excluded participation.

Measurement tools: As no previously developed or validated instrument was identified to describe a relationship between hormonal status and urinary tract function at night in women, a rapid review was performed. Items capturing lifestyle, menopausal and urogenital status, sexual dysfunction, gynaecological health, intervention for menopausal symptoms, dietary supplements

and intake of specific phyto-oestrogen food groups were collated into a study-specific *hormone status questionnaire* (Appendix S1).

The TANGO nocturia causality screening tool is a 4-domain metric capturing multiple and co-existing causes of night voiding (8). The measure has robust psychometric properties, is self-administered and easily interpreted (9). Hormonal depletion may be implicated in women with bothersome nocturia but is not currently captured by TANGO.

Finally, a paper version of the traditional three day, two night bladder diary was used. This is routinely collected at continence clinics and was not an added burden to participants. Seven measures were extracted from the bladder diary information (day, night and 24 hour urine volume, nocturia frequency, size of maximum day, night and overall void) and a further six variables derived (nocturnal polyuria index, day and night diuresis, nocturia index, predicted number of night voids and nocturnal bladder capacity index). The definitions of each of these data points are described in Table 1. Bladder diary measurements were derived separately by two clinicians using standardised definitions.

Although the International Continence Society defines nocturia as one or more voids during the main sleep period, for this study the clinically-relevant definition of at least two voids per night was applied and referred to throughout the text as “disruptive nocturia” (10). Nocturia frequency was collected in two ways: as an open-ended question (self-report), and by derivation of the number of episodes on a bladder diary (actual nightly voids). Global polyuria was defined as >3.0L of urine over 24 hours. Nocturnal polyuria (NP) was considered present when $\geq 33\%$ of 24-hour urine volume was produced during the main sleep period. A cut off value of >1.3 was used for the nocturia index (Ni) as this suggests that the volume of urine being produced overnight exceeds the 24 hour maximum bladder volume by sufficient to imply that nocturia is

related to excessive urine production. A cut-off value of >1.3 for nocturnal bladder capacity index (NBCi) indicates that nocturia is related to low bladder to store urine at night (11). Bladder capacity was considered reduced when average voided volumes were $<200\text{mL}$. Hormonal status was sub-classified as within one year since last menstrual period or more than one year since last menses.

Process: Upon recruitment women completed the study-specific hormone status questionnaire, the TANGO nocturia causality screening tool and provided a completed 3-day bladder diary. Age, gender and self-reported nocturia frequency were also obtained. Researchers did not access participants' medical records, investigation results or urinary tract treatment details.

Statistical Methods: The study was designed with a sample size to match that used in the development of the TANGO nocturia screening tool, predicated on the known prevalence of nocturia being 60% of people older than 65 years waking twice each night to pass urine. Selecting a confidence level of 80%, a significance level of 5% and a design effect of 1.0 we required a sample of 150 (12-13).

Data was extracted from the three study tools and entered into the Statistical Package for the Social Sciences (SPSS®, version 26.0, IBM Australia). Descriptive statistics were generated to summarise the age, gender, nocturia severity and time since last menstruation of the study sample overall. Endorsement of items on the study-specific hormone-status questionnaire and TANGO screening tool were tabulated using frequencies and percentages.

Bladder diary parameters between those endorsing / not endorsing the hormonal and lifestyle factors were explored using the Mann-Whitney U test and a two-sided significance level of 0.05. In women with nocturia (either by self-report $n=140$ or bladder diary record $n=130$),

endorsement of each of the hormone/lifestyle items was checked for association with disruptive nocturia using binary logistic regression. Regression models adjusting for known confounders (age, vaginal oestrogen treatment, systemic hormone replacement therapy) were run to identify factors predictive of disruptive nocturia, nocturnal polyuria index >33%, nocturia index > 1.3, and nocturnal bladder capacity index >1.3. 95% confidence intervals and significance levels were calculated.

Results

Study Participants

Mean age of the 153 study participants was 64.3 years (SD 12.1). With respect to hormonal status, 9% of women were still menstruating, 6% were within one year of their last menstrual period, 14% were between one and ten years post menses and 64% were at least ten years beyond menopause (7% missing data). Use of systemic hormone replacement therapy (HRT) or vaginal oestrogen was reported by 7.9% and 36% of women respectively. Half the women perceived themselves as being overweight; 29% of participants described their health as “not good”.

Nocturia was self-reported by 91.5% of the women. Overall, 55% of the sample self-reported disruptive nocturia (that is \geq two voids per night); this was confirmed in 42% of bladder diaries. The two measures of nocturia severity (self-report and ANV) demonstrated a moderate to strong positive correlation that was statistically significant ($r_s=0.64$, $p<0.001$).

Hormone Status Questionnaire

Overall, 40% of participants reported a known pelvic organ prolapse, half described loss of sexual interest, 30% identified as having night sweating and 28.5% reported day flushes. The extent to which the sample endorsed the hormonal and lifestyle factors from the Hormone Status Questionnaire is shown in Table 2. The most common interventions or self-help strategies were

physical activity, taking vitamin D, vaginal oestrogen therapy (cream or pessary), non-steroidal anti-inflammatory drugs (NSAIDs) and the use of probiotics.

TANGO Nocturia Screen

Data from the TANGO screening tool identified that 46% of women described their sleep quality as “bad”, 51% reported requiring >30 minutes to fall asleep (a symptom known as sleep onset latency) and 36% slept less than five hours each night. Overall, 56% of women with self-reported nocturia rose to void within 3 hours of going to sleep. Few participants (9%) described excessive daytime sleepiness (i.e. trouble staying awake while eating, driving or socialising). The proportion endorsing sleep disordered breathing item, voiding dysfunction, urinary urgency incontinence once per week and urinary urgency most days is shown in Table 2.

Hormone and Lifestyle Factors Associated with Nocturia

Table 3 shows the significant association between nocturia (both self-reported and actually nightly voids on bladder diary) and hormonal and lifestyle factors with $\geq 10\%$ endorsement, together with known confounders (age, vaginal oestrogen and systemic HRT). Entering the items with a significance level of $p \leq 0.200$, and the expected confounders into a regression model for self-reported disruptive nocturia returned two independent predictors, age (OR 1.04, $p=0.038$) and vitamin D supplementation (OR 2.33, $p=0.026$). Night sweating was associated with double the likelihood of reporting nocturia of at least two per night (OR 2.25, $p=0.052$). The logistic regression model for self-reported disruptive nocturia was statistically significant, chi-square = 15.85, $p=0.015$.

There was a discrepancy in nocturia frequency, in that 13 women who did not self-report nocturia recorded night voiding on their bladder diaries, while 17 women who self-reported nocturia recorded no nightly voids. The overall regression model for at least two nocturia episodes documented on the bladder diary was statistically significant (chi-square=14.63, $p=0.023$). Two of the six predictor variables were independently significant. Self-reporting

flushes during the day was associated with 2.7 times the odds of disruptive nightly voids (OR 2.67, $p=0.025$) whereas regular exercise reduced the risk of disruptive nocturia by 60% (OR 0.38, $p=0.012$).

Hormone and Lifestyle Factors Associated with Other Bladder Parameters

Table 4 shows the change in the median value of actual nocturia episodes and derived bladder parameters associated with endorsement of hormonal and lifestyle factors. The number of nocturia episodes per night was unaffected by intake of phyto-oestrogen food, overweight status, urogenital prolapse, loss of sexual interest or vaginal dryness. Bladder diary parameters were unchanged by use of probiotics, non-steroidal anti-inflammatory medications, vaginal oestrogen or the presence of night sweating. However, significant differences in median bladder diary parameters emerged when women reported day flushes, prolapse, vitamin D supplementation and engaged in more than 150 minutes of general exercise per week.

Relative contribution of urine production and bladder storage

Global polyuria was identified in 8.5% of the sample; there was no statistically significant difference in median 24-hr urine volume between participants with disruptive versus single episodes of nocturia (1945mL vs 1618m, $p=0.353$).

Excessive night urine volume (suggested by nocturia index > 1.3) was noted in 77.7 % of women; significantly more common with disruptive nocturia (95.3%) compared to one void at night (60.6%; $p<0.001$). Nocturnal polyuria was evident in 64.6% of participants; 51.5% with one void / night and 78.1% of those with disruptive nocturia. A significantly higher proportion of individuals with disruptive nocturia had NP as compared to women voiding less often at night (chi square = 10.06, $p=0.002$). Overall, 23.1% of participants produced > 90 mL urine / hour of sleep; the correlation between diuresis rate at night and nocturia severity was positive and significant, although weak ($r=0.23$, $p=0.009$).

There was a significant difference of 167.5 mL ($p=0.001$) in nocturnal urine volume (NUV) between women with disruptive nocturia (median 685mL) and those with less nocturia (517.5mL). The logistic regression model for nocturia index > 2 (i.e. excessive night urine) was significant (chi square =30.52, $p<0.001$). Four of the eight predictor variables were independent predictors: i) Age – OR 1.06, 95%CI 1.026-1.105; ii) flushes during the day – OR 2.96, 95% CI 1.250-7.029
iii) 150 minutes of exercise per week – OR 0.30, 95% CI 0.134-0.638 and iv) use of HRT – OR 0.18, 95% CI 0.032-0.990.

The logistic regression model for nocturnal polyuria (i.e. NPi $>33\%$) was significant (chi square =35.82, $p<0.001$). Of the eight predictor variables (age, vaginal oestrogen use, HRT, vitamin D intake, day flushes, night sweating, prolapse and at least 150 minutes of exercise per week) two were independently significant. Each additional year of age increased the odds of nocturnal polyuria by 7% (OR 1.07, 95% CI 1.027-1.111), while exercise was protective (OR 0.22, 95% CI 0.093-5.488).

Voided volume on bladder diary was reduced globally (10%), at night (17%) and during the day (37%). Maximum voided volumes were significantly lower for participants with disruptive nocturia compared to other women (Night: 268ml vs 350mL, $p=0.006$; Day: 200mL vs 290mL, $p<0.001$).

Nocturia potentially attributable to overactive bladder (i.e. where NBCi > 1.3) was observed in 26.2% of the cohort. NBCi was significantly higher with disruptive nocturia compared to a single night void (1.26 vs 0.46, $p<0.001$). Of the five predictors identified on univariate analysis, only report of flushes during the day was statistically significant for NBCi >1.3 : these women

were 2.8 times more likely to have an NBCi>1.3 (95% CI 1.216-6.615). However, the logistic regression model itself was not significant (chi square = 8.77, p=0.187).

As per Table 4, it can be seen that significant associations were demonstrated between flushes during the day and number of nightly voids, although the clinical effect was modest. There was also a 45% increase in nocturnal bladder capacity index in women reporting daytime flushing. Associations between overnight urine volume and vitamin D supplementation were also observed. A cross sectional study cannot attribute causality, therefore these findings alone may be insufficient to justify adding items to the TANGO nocturia screening tool. An item capturing oestrogen supplementation either systemically or vaginally, may be warranted.

Discussion

Main findings.

This study provides new data regarding disruptive nocturia in women 40 years and older, particularly as regards hormonal factors. At least 51% of the women with nocturia and 78% who voided twice per night demonstrated nocturnal polyuria (when the cut-off of 33% of 24-hour urine volume was applied), confirming an increased nocturnal diuresis rate and total overnight volume in these women. Poor bladder storage was also implicated, as nocturia of at least twice per night was significantly associated with low voided volumes both during the day and at night. Furthermore, as shown by significantly higher NBCi, women voiding multiple times at night did so at volumes less than their own maximum. Thus, disruptive nocturia in post-menopausal women can be considered to have a mixed pathophysiology.

Of interest to gynaecologists is the finding that disruptive nocturia could potentially be exacerbated by both urogenital prolapse and thermoregulation difficulties during the day. Low oestrogen may modulate the endocrine or parasympathetic nervous systems or be adjunctive to

connective tissue changes that underlie pelvic organ prolapse (14,15). Although we could not demonstrate a previously reported association between prolapse and nocturia severity (16) the novel finding from this study was that self-reported prolapse may increase nocturnal diuresis and urine volume.

Hot flushes during the day was significantly associated with both severity of nocturia and the proxy for overactive bladder, NBCi >1.3, potentially explaining half an episode of night voiding. This may interplay with the predictive protective effect of HRT on the nocturia index. It is unclear why night sweating did not show a similar association with nocturia severity, unless the effect was modulated by learned urinary frequency in response to urgency. From a clinical perspective, since both prolapse and hot flushes are amenable to treatment, and have the potential to impact underlying causes of nocturia, inclusion in a management bundle of care may be warranted.

Less expected was the finding that vitamin D supplementation was associated with increased nocturnal diuresis. Vitamin D is known to play an important role in water and salt homeostasis, possibly through an effect on the expression of aquaporins, specifically those that regulate the water channels and affect urine concentration (17-18). Alternatively, vitamin D intake may potentiate hypercalcaemia or induce a secondary renal concentrating defect relevant to overnight diuresis (19, 20). Given that vitamin D levels and therapeutic supplementation are not described in the aetiology of nocturia, nor routinely investigated during clinical care of the woman with bothersome nocturia, the area warrants closer investigation (14, 21).

It is recognised that the genitourinary syndrome of menopause includes urinary frequency, nocturia, urinary urgency, stress incontinence and urinary tract infections, and that treatments can improve function and quality of life (7,22). In this study, women who reported using either

systemic HRT (8%) or vaginal oestrogen (36%) were not protected from bothersome nocturia, with both therapies failing to demonstrate a significant association with nocturia frequency by either self-report and bladder diary entry. However, this was not a cross-sectional study, nor did it collect adherence to regular use of either hormonal supplementation, therefore impact of either therapy could not be evaluated. Given that vaginal oestrogen over the long term has been shown to have a low risk profile (22), research into its role in overall management of nocturia in postmenopausal women is justified.

The women in this study were relatively young, non-obese and at least 70% were free of major health issues. In this sample, participating in a level of physical activity equivalent to 150 minutes per week, as recommended in guidelines issued by the Australian government (23), was protective for nocturia frequency, bladder storage and urine production during the night. Given that this was not an overweight population it is doubtful the effect can be explained by impact on metabolic rate. Engagement of the lower limb muscle pumps during exercise may reduce third space sequestration or alternatively maintain cardiac function and fitness. Engaging in 150 minutes of exercise per week reduced nocturia by half an episode and reduced the risk of clinically relevant nocturnal polyuria by 78%. Anti-diuretic therapy, by comparison, decreases nocturnal excretion of “free water”, reducing nocturia by at least 1.4 episodes/night and nocturnal urine production by 300ml (24).

There was a significant protective impact of regular physical exercise on NBCi, suggesting an increased bladder storage at night. Patients with nocturia who respond to pharmacological treatment for overactive bladder syndrome generally report only a modest reduction in nocturia episodes, not appreciably different from placebo (25). Overactive bladder medication has been reported to reduce nocturia by <0.2 episodes (11). Clearly, the clinical application that physical

activity in women is protective for both nocturia frequency and urine production parameters, is a potential adjunct intervention and warrants further investigation.

Limitations

Several limitations are noted in the current study, principally that there is a clear selection bias in the population of women presenting to the continence services involved. Additionally, subjective and patient-reported measures were used, introducing possible recall and other biases. The work was cross-sectional in design, precluding investigation of any causal relationships. Future studies in the clinical environment might include blood markers of vitamin D and oestrogen levels, pelvic organ prolapse measurements alongside a record of individual co-morbidities and their concurrent management.

Interpretation

Multi-modal therapy is common practice for lower urinary tract symptoms, integrating behavioural, lifestyle and pharmacological interventions to target different causal pathways. Findings from this study support testing a multi-modal care bundle of interventions for nocturia in women. The addition of >150 mins exercise, prolapse management and oestrogen replacement to current therapy for bothersome nocturia (i.e. bladder training, behavioural strategies and anti-diuresis) could be tested in a controlled study. Use of available smart bladder diary application technology will reduce participant burden, increase clinician access to bladder measures and facilitate data analysis (26).

Earlier work confirmed multiple relationships between nocturia and non-lower urinary tract markers of impaired health, knowledge that was translated into the TANGO causality screening tool capturing possible underlying causes of voiding at night (8). The present study has provided insight into the need for additional items that capture the impact of hormonal depletion on the causal pathways in individual women with bothersome nocturia. Two changes are proposed: the

310 use of hormone replacement in any form as a proxy for depletion symptoms, and the addition of
311 “prolapse” as a gendered alternative in the voiding dysfunction item.

312

313 **Conclusion**

314 Nocturia in post-menopausal women is associated with changes to both nocturnal diuresis and
315 bladder storage. Flushes during the day was predictive of both overnight urine volume and also
316 bladder storage suggestive of overactive bladder. The possibility that nocturia can be induced by
317 vitamin D supplementation warrants closer scrutiny. Regular physical activity, prolapse
318 reduction and oestrogen replacement may be adjunctive in managing bothersome nocturia in
319 women.

320

321 **Disclosure of interests**

322 The authors have no conflicting interests to disclose

323

324 **Contribution to authorship**

WF Bower	Protocol Development, Data Collection, Data Analysis, Interpretation of Findings, Manuscript Preparation
GE Rose	Data analysis, Interpretation of Findings, Manuscript Preparation
DM Whishaw	Data Collection, Manuscript Preparation
CF Ervin	Data Collection, Manuscript Preparation
A Wang	Protocol Development, Data Collection
KH Moore	Protocol Development, Data Collection, Interpretation of Findings, Manuscript Preparation

325 **Details of ethics approval**

326 The study was approved by the Human Research Ethics Committee at each participating
327 institution (i. HREC/17/MH/392; ii. 18/G/086 iii.18/WMEAD/272)

328

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