Title:

TANGO – a screening tool to identify comorbidities on the casual pathway of Nocturia

Authors:

W.F. Bower, G.E. Rose, C.F. Ervin, J. Goldin, D.M. Whishaw and F. Khan

Journal:

BJU Int 2017

BJUI
BJU International

Functional Urology

TANGO – a screening tool to identify comorbidities on the causal pathway of nocturia

Wendy F. Bower*†, Georgie E. Rose‡, Claire F. Ervin†, Jeremy Goldin‡, David M. Whishaw§¶ and Fary Khan*

*Department of Rehabilitation, †Sub-Acute Community Services, ‡Department of Respiratory and Sleep Medicine, §Department of Aged Care, and ¶Department of Urology, Royal Melbourne Hospital, Parville, Vic., Australia

Objectives

To develop a robust screening metric for use in identifying non-lower urinary tract comorbidities pertinent to the multidisciplinary assessment of patients with nocturia.

Methods

Variables having a significant risk association with nocturia of greater than once per night were identified. Discriminating items from validated and reliable tools measuring these comorbidities were identified. A self-completed 57-item questionnaire was developed and a medical checklist and pertinent clinical measures added. Pre-determined criteria were applied to retain or remove items in the development of the Short-Form (SF) screening tool. The tool was administered to 252 individuals with nocturia who were attending either a tertiary level Sleep, Continence, Falls or Rehabilitation service for routine care. Data collected were subjected to descriptive analysis; criteria were applied to reduce the number of items. Using pre-determined domains, a nocturia screening metric, entitled TANGO, was generated. The acronym TANGO stands for *Targeting the individual's Aetiology of Nocturia to Guide Outcomes*.

Results

The demographic characteristics of the sample are described, along with item endorsement levels. The statistical and structural framework to justify deleting or retaining of items from the TANGO Long-Form to the SF is presented. The resultant TANGO-SF patient-completed nocturia screening tool is reported.

Conclusions

A novel all-cause diagnostic metric for identifying co-existing morbidities of clinical relevance to nocturia in patients who present across disciplines and medical specialties has been developed. TANGO has the potential to improve practice and smooth inequalities associated with a siloed approach to assessment and subsequent care of patients with nocturia.

Keywords

nocturia, aetiology, diagnosis, Targeting the individual's Aetiology of Nocturia to Guide Outcomes, screening

Introduction

Individual causes are unlikely to be sufficient or necessary to produce nocturia [1]; multiple 'backdoor' causal pathways are common. Although solid evidence exists that factors such as prostatic enlargement and nocturnal polyuria are linked to a high frequency of nocturia, waking to void is likely to represent an interaction of causes, often outside the urinary tract system [2–4]. Given that episodes of nocturia are more often seen in individuals with poor or fair health than in people reporting a good health status, the symptom itself may be a surrogate marker of impaired wellbeing.

Common practice in patients with nocturia is to identify relative polyuria at night, as a proportion of total 24-h urine production, detect prostatic enlargement, ascertain the presence of bladder overactivity, and observe the lower legs for evidence of peripheral oedema [5,6]. Each of these factors can be causative of nocturia and warrant examination. However, the greatest risks attached to frequent nocturia appear to be where dysfunctions co-exist i.e., individuals either using sedatives or complaining of secondary insomnia who also report falls, women with a poor health status or disordered breathing, anxiety or impaired cognition as a co-morbid diagnosis in either gender, the presence of both restless leg syndrome and secondary insomnia, and men with nocturia who also have elevated inflammatory markers [1]. The possible combinations of co-existing symptoms cross disciplines and system-specific expertise.

 | doi:10.1111/bju.13774
Published by John Wiley & Sons Ltd. www.bjui.org

Patients may not proffer the symptom of nocturia at a medical appointment for a systemic or unrelated disorder, believing it to be trivial and not worth reporting [7]. This belief does not align with older people reporting frustration, a negative impact on quality of life, tiredness, inconvenience and reduced function as a result of nocturia [8]. Nor does it reflect the personal and healthcare costs associated with nocturia. Under-reporting of nocturia may reveal a taboo around waking at night to void and indicate that the symptom is ubiquitous or considered a hallmark of ageing.

In reality, patients with nocturia are more likely to present with complex medical issues than with nocturia as a single symptom of concern. Clinicians are well aware that unmanaged nocturia carries significant morbidity, even when stratified for age and known risk factors. To ensure best care for patients with nocturia, health professionals need to be confident that all possible causes of the symptom have been identified. There is currently no screening instrument or diagnostic pathway for nocturia that includes evaluation of relevant dysfunction in multiple body systems. A clinical tool that captures information about aspects of nocturia and causal comorbidities is necessary.

The aim of the present study was to develop a brief patient-completed screening tool for use in identifying potential and co-existing causes of nocturia. The metric was required to capture clinically relevant variables, critical items that may show a low level of endorsement and questions representative of the breadth of implicated domains. Furthermore, the screening metric should contain items from validated tools.

Methods

We have previously described a literature search undertaken to identify studies clarifying the relationships between nocturia of ≥1/night and markers of poor health, and reported significantly associated risk factors [1]. In developing the Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO) screening tool, the previously identified domains of health status, mental health, cardiovascular, metabolic, inflammation, and sleep disorders were utilised. The index question established the frequency of nocturia at night and the bother this caused.

Materials

Validated and reliable patient-completed instruments that captured the presence of variables specific to each domain, and that were significantly associated with nocturia, were identified [9]. Given that retaining all items from the separate validated measures in the screening tool was unwieldy, a clinical judgement discrimination process was undertaken. Individual items were scrutinised to identify questions relevant to nocturia or that could be considered key discriminators of different health system domains. Items that were non-specific or duplicated in other tools were not selected. Questions for each domain were extracted separately from the different tools, combined and grouped together in the long version of the TANGO screening form. In summary, questions included on the TANGO Long-Form (LF) were selected from a number of robust measures of other health issues and grouped under the domains of interest to nocturia (i.e. cardiovascular/metabolic dysfunction, sleep issues, urinary tract symptoms, wellbeing). Clinical measures indicative of associated risk factors were identified and similarly scrutinised: height; weight; blood pressure in supine, sitting and standing; heart rate; hip, waist and neck size; and walking speed using the 'Timed Up and Go' test, were added to the screening form. Content validity was established by cross checking the domain-specific items of each of the identified pre-existing validated metrics against the variables in the TANGO-LF. This process has been previously described [9].

Pilot testing of the final version of TANGO-LF was conducted in 20 individuals and included cognitive interviewing of five respondents. The process revealed no issues with the measure. After pilot testing, the TANGO-LF comprised 57 questions and 10 clinical measures.

Population

Psychometric analysis traditionally obtains precision of estimates from a sample size of ~250 data sets; however, our tool was not designed to give a total score and therefore did not require a specific number of subjects. Instead, we selected participants representative of mid to older aged adults with nocturia who would have the characteristics of patients the screening tool is intended to be used with. The study recruited 252 individuals aged ≥40 years who woke at night to void and who were presenting for care at the Royal Melbourne Hospital Continence, Rehabilitation, Falls and Balance or Sleep Disorders outpatient clinics, or, who were inpatients on either the Aged Care or Rehabilitation wards. Clinical services involved in the study reflected the target population who have nocturia. The eligibility age of 40 years was selected to include capture of data from the typical population attending for assessment of sleep apnoea.

Individuals with any of the following conditions that may be associated with atypical nocturia were ineligible for inclusion: receiving end-of-life care, terminal malignancies, end-stage renal disease, bladder cancer, previous pelvic radiotherapy, pregnancy, dementia requiring supervision, or cognitive impairment that precluded questionnaire completion. Similarly, individuals who were medically unstable were excluded from the study.

Process

The study was ratified by Melbourne Health Human Research Ethics Committee (EC00243); approval number LNRSSA/16/MH/64. Patients registering for a hospital clinic appointment in any of the participating services within our institution were handed a flyer by clerical staff describing the prospective questionnaire study. If during their healthcare appointment they reported an interest in participating in the study, the patient information material and consent form were presented. Study staff then explained the process for self-completing the questionnaire and permitting the 10 physical measures. The time burden estimated was ~15 min. Individuals agreeing to participate in the study signed a written consent form. Participants completed the TANGO questions and physical measurements before leaving the hospital.

As the TANGO-LF was anonymous no attempt was made to link participant's data sets with medical record details of concurrent illness. De-identified coded data were entered into a tailored password-protected database.

Statistical Analysis

Data were analysed using the Statistical Package for the Social Sciences (SPSS®, version 23, Australian Head Office, IBM Australia Ltd, St Leonards, NSW, Australia); demographic, social and physical characteristics of the sample were tabulated. Endorsement of items was investigated; those with a high floor effect (i.e. >70% of responses 'never' or its equivalent), an inter-relationship >0.6 or >20% missing data were noted.

The association between individual items and severity of nocturia was established using univariate linear regression. Discrete items were analysed separately; however, where items were part of an index, corrected item correlation was used to rank the individual items. The dependent variable of nocturia frequency was considered both as a continuous variable and as a binary value (nocturia <2 voids/night vs nocturia ≥2 voids/night). A logistic regression model to assess the impact of significant univariate associations on the likelihood of nocturia frequency of ≥2 voids/night was built.

Conceptual as well as empirical and clinical factors were considered when assessing items for inclusion or exclusion in the TANGO Short-Form (SF). Missing responses and endorsement levels were included in the decision process, but subject to clinical judgement. The decision whether or not to retain items in the TANGO-SF was the result of a process whereby items were retained if they were on a direct causal pathway to nocturia, demonstrated a significance of association with high nocturia frequency, showed high endorsement, evidenced no floor effect, and were not highly correlated with other items. All variables were evaluated for these factors; items failing the criteria were removed. The TANGO-SF was built from retained items re-grouped into the four previously specified domains.

Results

Sample

Table 1 summarises the demographic details of participants in the study and shows the mean (SD) age of the participants to be 65 (12) years. Overall the gender split was even, although females predominated in the Continence service and males in the Sleep clinic. Only two participants were identified as indigenous to Australia, New Zealand or the Pacific Islands. Education to the level of senior high school or below was reported by half the sample. Close to two-thirds of participants resided in an area classified as disadvantaged.

Physical attributes reported in Table 2 indicate that participants were overweight and that metabolic risk, as indicated by an elevation in gender-specific waist–hip ratio, was high in women but borderline for men. Hypertension was reported by half the sample in the questionnaire but was within normal limits when measured. One quarter of participants exhibited postural hypotension. Diabetes mellitus was reported by 30% of participants.

Overall 19% of participants reported 'excellent' or 'very good health', whilst 45% summarised their health status as 'fair' or 'poor'. A history of cancer was reported by 16% of participants. Just over half the participants (54%) reported being in moderate or severe pain or discomfort and 63% identified as having limited mobility. Parkinson's disease and multiple sclerosis were reported by 5% and 8% of the participants, respectively. About one-third of the cohort described a fall within the preceding 3 months.

Frequency of nocturia ranged from one to 11 voids with a mean (SD) of 2.5 (1.4) voids/night. Figure 1 shows that more nocturia episodes were non-significantly associated with incremental age across the cohorts. Bother related to nocturia showed a linear relationship with frequency of episodes, with 3 voids/night being moderately bothersome (Fig. 2).

TANGO-LF Items

Endorsement scrutiny revealed poor completion of items related to the participant working outside the home or being a carer, retiree, or living alone (29%, 33%, 17%, 29% missing respectively). None of these items were significantly associated with nocturia severity. Other items with >10% missing data included: kicking legs during sleep, uncomfortable breathing or snoring disrupting sleep, sleep apnoea, problematic leg

Table 1 Demographic characteristics of the participants in the study.

Characteristic	Overall	Continence clinic patients	Sleep clinic patients	Other services patients*
No. of patients (%)	252 (100)	107 (42.5)	100 (39.7)	45 (17.9)
Age, years, mean (SD)	64.8 (12.8)	68.14 (12.7)	59.17 (10.7)	69.2 (13.2)
N (%)				
Gender				
Male	125 (49.6)	38 (35.5)	60 (60.0)	27 (60.0)
Female	126 (50.0)	68 (63.6)	40 (40.0)	18 (40.0)
No response	1 (0.4)	1 (0.9)	0	0
Age group, years				
40–49	42 (16.7)	15 (14.0)	22 (22.0)	5 (11.1)
50–59	41 (16.3)	12 (11.2)	26 (26.0)	3 (6.7)
60–69	75 (29.8)	28 (26.2)	33 (33.0)	14 (31.1)
70–79	56 (22.2)	28 (26.2)	18 (18.0)	10 (22.2)
≥80	38 (15.1)	24 (22.4)	1 (1.0)	13 (28.9)
Education level				
Middle School or below	75 (29.8)	29 (27.1)	28 (28.0)	18 (40.0)
Senior High School	59 (23.4)	31 (29.0)	18 (18.0)	10 (22.2)
Trade/vocational	55 (21.8)	24 (22.4)	24 (24.0)	7 (15.6)
University or above	58 (23.0)	20 (18.7)	28 (28.0)	10 (22.2)
No response	5 (2.0)	3 (2.8)	2 (2.0)	0
Living status				
Alone	65 (25.8)	28 (26.2)	23 (23.0)	14 (31.1)
No response	91 (36.1)	34 (31.8)	25 (25.0)	32 (71.1)
Working status				
Working	65 (25.8)	22 (20.6)	37 (37.0)	6 (13.3)
Retired/not working	114 (45.2)	49 (45.8)	43 (43.0)	22 (48.9)
No response	84 (33.3)	36 (33.6)	20 (20.0)	28 (62.2)
IRSAD†				
Lowest 40%	89 (35)	39 (36.4)	39 (39)	11 (24.4)
No response	5 (2.0)	3 (2.8)	0	2 (4.4)

**Other Services: Rehabilitation, Falls and Balance Clinic, Rehabilitation Ward, Aged Care Ward. †IRSAD, Index of Social Advantage and Disadvantage [19].*

Table 2 Physical characteristics of the participants in the study.

	Overall (*n* = 252)	Continence clinic patients (*n* = 107)	Sleep clinic patients (*n* = 100)	Other services* patients (*n* = 45)
BMI, kg/m^2, mean (SD)	*n* = 243	*n* = 103	*n* = 98	*n* = 42
	31.2 (7.5)	29.3 (6.0)	34.1 (7.9)	29.2 (7.7)
Waist–hip ratio, mean (SD)				
Male	*n* = 122	*n* = 36	*n* = 60	*n* = 26
	1.0 (0.07)	0.98 (0.07)	1.02 (0.07)	0.96 (0.06)
Female	*n* = 120	*n* = 67	*n* = 37	*n* = 16
	0.90 (0.07)	0.90 (0.07)	0.90 (0.05)	0.91 (0.05)
Systolic blood pressure, mmHg, mean (SD)	*n* = 237	*n* = 104	*n* = 92	*n* = 41
	132 (18.4)	135.4 (20.8)	129.7 (16.5)	133.3 (14.8)
Diastolic blood pressure, mmHg, mean (SD)	*n* = 237	*n* = 104	*n* = 92	*n* = 41
	77.36 (9.6)	77.2 (9.0)	77.5 (10.8)	77.5 (8.6)
Evidence of postural hypotension, *n* (%)	n = 252	*n* = 107	*n* = 100	*n* = 45
	56 (22.2)	19 (17.8)	25 (25)	12 (26.7)
'Timed Up and Go' test, s, median (IQR)	*n* = 223	*n* = 103	*n* = 84	*n* = 36
	10.0 (8.0–14.3)	10.3 (8.0–15.0)	10.1 (8.0–13.5)	9.1 (7.2–9.1)

**Other Services: Rehabilitation, Falls and Balance Clinic, Rehabilitation Ward, Aged Care Ward.*

veins, using medication to calm the brain, and the 'Timed Up and Go' test. Most items showed ~2% missing values.

Table 3 describes the structural framework used to evaluate individual items in the TANGO-LF. It can be seen that 22 items were significantly associated with a higher frequency of nocturia episodes ($P < 0.05$). Medical issues that warranted inclusion regardless of either the level of endorsement or floor effects were kidney dysfunction; the presence of, or poorly controlled, hypertension or diabetes; the use of diuretic medication; and persistent lower limb fluid

Fig. 1 Frequency of nocturia in continence and sleep patients.

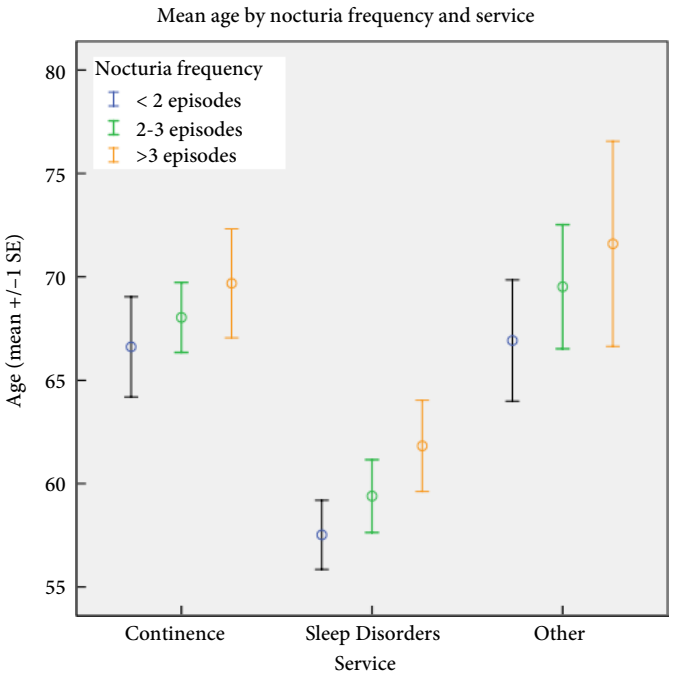
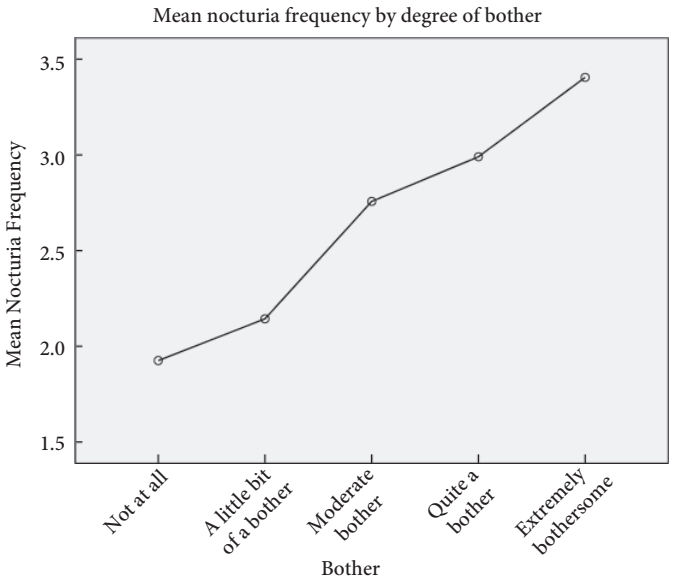


Fig. 2 Relationship between nocturia frequency and degree of bother.



accumulation. Of these, the mean number of nocturia episodes was significantly higher in participants with kidney disease ($P = 0.016$), hypertension ($P = 0.040$), lower leg oedema ($P = 0.01$), and marginally significant in participants using diuretic medication ($P = 0.056$).

Figure 3 shows the decision tree underlying whether or not to retain items in the TANGO-SF; the process resulted in 20 items, including one physical measure being retained. As the TANGO-SF was designed to be a self-completed tool, the physical measure – 'Timed Up and Go' test (time predictive of increased risk of falling) – was replaced with the item history of any falls. Two further clinically important items, known prostatic enlargement and poor glycaemic control, were included. Appendix 1 shows the resulting 22-item TANGO-SF, with items grouped under the domains of cardiovascular or metabolic disorders, sleep conditions, urinary tract symptoms and wellbeing.

The regression model for high frequency nocturia contained eight independent variables: general health, pain, time to first nocturia, sudden urgency, urgency incontinence, depression, hours in bed, and sleep quality. The full model was statistically significant (chi square [13, $N = 227$] = 77.47, $P < 0.001$), indicating that the model was able to distinguish between respondents who reported nocturia frequency of <2 voids/night and those who reported nocturia frequency of ≥2 voids/night. The model as a whole explained between 28.9% (Cox and Snell R^2) and 40.3% (Nagelkerke R^2) of the variance in nocturia frequency, and correctly classified 78.9% of all cases (90.2% of individuals with nocturia frequency of ≥2 voids/night).

Three of the independent variables made a unique statistically significant contribution to the model (time to first nocturia episode, urgency incontinence, and sudden urgency). The strongest predictor of nocturia frequency of ≥2 voids/night was urgency incontinence, with an odds ratio of 2.52. This indicates that individuals who experience urgency-related incontinence daily or more often are 2.52 times more likely to report a nocturia frequency of ≥2 voids/night, controlling for all other factors in the model. The odds ratio of 0.47 for time to nocturia indicates that for every additional minute of sleep before waking, individuals are 0.47-times less likely to report a nocturia frequency of ≥2 voids/night.

Discussion

A simple patient-completed screening form has been developed from variables significantly associated with an increased risk of nocturia. Data from two different clinical cohorts representative of patients with nocturia has been subjected to mixed-method scrutiny to identify multiple non-lower urinary tract variables on the causal pathway of night voiding. The TANGO-SF will increase capture of these comorbidities in clinical practice at no expense to time or cost.

Using the domains identified in our previous work, cardiovascular or metabolic disorders, sleep variables, urinary tract symptoms, and mental health and wellbeing, items in TANGO are grouped for quick interpretation. Domains can be switched in and out depending on the clinical context. For example, a GP will be fully aware of an individual patient's cardiovascular and metabolic status, sleep physicians will have captured the salient aspects of insomnia, and a continence clinician will be conversant with LUTS. The TANGO-SF can

Table 3 Evaluation grid justifying items retained in the TANGO-SF.

Variable	Univariate linear regression with nocturia frequency, R^2 (P)	Clinically important value/score	Responses with clinically important score, %	Floor effect: proportion of non-problematic option endorsed, %	Missing data, n (%)	Inter-correlations between predictor variables
Demographic						
Age	0.020 (0.023)	–	–	–	1 (0.4)	–
Physical measures						
Neck girth, cm	0.001 (0.717)	≥43 in males	54.03	–	1 (0.4)	–
		≥41 in females	21.67		6 (2.4)	
Waist girth, cm	0.000 (0.757)	≥102 in males	74.8	–	2 (0.8)	–
		≥88 in females	86.0		5 (2.0)	
Waist–hip ratio	0.000 (0.772)	>1.0 in males	50.0	–	3 (1.2)	–
		>0.85 in females	82.5		6 (2.4)	
Weight	0.002 (0.486)	–	–	–	7 (2.8)	–
Body mass index, kg/m^2	0.000 (0.996)	≥30 – moderately to very severely obese	53.5	–	9 (3.6)	–
'Timed Up and Go' test, s	0.052 (0.001)	>13.5 – increased risk of falling	28.3	–	29 (11.5)	–
Wellbeing						
General health	0.037 (0.002)	Fair to poor health	45.4	22.7	1 (0.4)	Spearman's ρ 0.392, $P < 0.001$ with pain/discomfort
Pain/discomfort	0.024 (0.015)	Moderate to severe pain/discomfort	54.3	20.9	3 (1.2)	See general health and sleep pain
Any Falls	0.005 (0.278)	Yes to any falls	29.0	71	0 (0)	–
Cardiovascular/metabolic						
Leg swelling	0.027 (0.010)	Yes to leg swelling	49.8	50.2	3 (1.2)	See hypertension, kidney disease and fluid medications
Hypertension	0.014 (0.070)	Yes to hypertension	53.7	46.3	8 (3.2)	Pearson's r 0.171, $P = 0.008$ with leg swelling
Kidney disease	0.025 (0.017)	Yes to kidney disease	7.7	92.3	19 (7.5)	Pearson's r 0.139, $P = 0.035$ with leg swelling
Diabetes/high blood sugar level	0.005 (0.251)	Yes to diabetes or high blood sugar level	30.3	69.7	8 (3.2)	–
Fluid medications	0.016 (0.056)	Yes to diuretics	18.8	81.2	23 (9.1)	Pearson's r 0.130, $P = 0.050$ with leg swelling
Heart rate at rest, beats/min	0.001 (0.647)	≥100	1.6	–	8 (3.2)	–
		<60	9.0			
Urinary tract						
Time to nocturia, h	0.144 (0.001)	<3 h	40	4.1 (>6 h)	12 (4.8)	–
Sudden urgency	0.085 (<0.001)	Daily or more often	64.4	16.4	2 (0.8)	Pearson's r 0.485, $P < 0.001$ with urgency incontinence
Strain (MEN ONLY)	0.059 (0.007)	Sometimes or often	32.5	52.0	2 (0.8)	–
Urgency incontinence	0.051 (<0.001)	Daily or more often	40.9	37.3	3 (1.2)	See sudden urgency
Anxiety and depression						
Worried	0.002 (0.447)	A lot of the time to a great deal of time	24.3	37.7	5 (2.0)	–
Nervous	0.009 (0.136)	Quite often to very often	8.5	52.2	5 (2.0)	–
Restless	0.002 (0.518)	Quite a lot to very much indeed	29.8	31.8	7 (2.8)	–
Enjoyment	0.03 (0.006)	Only a little to hardly at all	19	36.7	4 (1.6)	–
Laugh	0.01 (0.120)	Not so much to not at all	10.1	59.5	5 (2.0)	–
Cheerful	0.020 (0.028)	Not often to not at all	14.1	53.2	4 (1.6)	–
Slowed	0.008 (0.163)	Very often to nearly all the time	48.2	7.7	5 (2.0)	–
Disinterest (in appearance)	0.019 (0.031)	I don't take care	22.9	48.8	4 (1.6)	–
Optimism	0.036 (0.003)	Less/hardly at all	23.3	47.6	4 (1.6)	Spearman's ρ 0.608, $P < 0.001$ with HADS depression

Table 3 (continued)

Variable	Univariate linear regression with nocturia frequency, R^2 (*P*)	Clinically important value/score	Responses with clinically important score, %	Floor effect: proportion of non-problematic option endorsed, %	Missing data, *n* (%)	Inter-correlations between predictor variables
Enjoy activity	0.013 (0.072)	Not often/seldom	6.4	65.7	4 (1.6)	–
HADS anxiety	0.011 (0.109)	11–21 'abnormal'	16.5	–	9 (3.6)	–
HADS depression	0.046 (0.001)	11–21 'Abnormal'	11.4	–	6 (3.6)	See optimism
Sleep						
Staying asleep	0.100 (<0.001)	Often to always	42.3	24.4	18 (7.1)	Spearman's ρ 0.544, $P < 0.001$ with sleep quality
Time to sleep, min	0.051 (<0.001)	>30	24.2	5.8 (<5 mins)	12 (4.8)	Pearson's r 0.214, $P = 0.001$ with sleep quality
Hours in bed	0.018 (0.033)	<6	2.4	–	4 (1.6)	Spearman's ρ −0.031, $P = 0.624$ with sleep quality
		>10	16.9			
Hours of sleep	0.035 (0.003)	<6	35.1	5.7 (<4 h)	7 (2.8)	Spearman's ρ −0.517, $P < 0.001$ with sleep quality
		>8	13.1			
Sleep pain	0.041 (0.001)	Weekly or more often	41.7	43.8	10 (4.0)	Spearman's ρ 0.572, $P < 0.001$ with pain/discomfort
Sleep quality	0.071 (<0.001)	Fairly bad to very bad	33.1	12.9	4 (1.6)	See staying asleep, time to sleep, hours in bed and hours of sleep

Fig. 3 Decision tree for generating items to be retained in Targeting the individual's Aetiology of Nocturia to Guide Outcomes (TANGO)-Short-Form (SF).

1. TANGO Long Form: 57 questions; 10 physical measures.
2. Removal of demographic items designed for descriptive analyses only.
3. Removal of items with poor endorsement (>20% missing data).
4. Removal of items with a high floor effect (>70% responses 'never' or its equivalent).
5. Removal of items of low clinical relevance and/or those non-significantly associated with nocturia severity.
6. Removal of redundant items showing high agreement with other items (i.e an inter-relationship > 0.6)
7. TANGO Short Form; 22 statements across 4 domains

be modified for each cohort or left in its entirety for use in a broader clinical setting.

Multiple comorbidities relevant to the aetiology of frequent nocturia can be captured by TANGO, facilitating comprehensive evaluation for co-existing causes traditionally beyond the scope of LUTS. Clinicians then have the basis for a bundled treatment approach to nocturia, by investigating and intervening for clinically relevant co-existing dysfunction. Use of TANGO may uncover for example, the need for a sleep assessment, a diabetic review, pain management or intervention for depression, all of which directly or indirectly impact the production and storage of urine overnight.

As an assessment tool for nocturia, TANGO sits alongside the evaluation of 24-h urine production and specifically the proportion of urine generated overnight. It has been observed that the severity of nocturia correlates poorly with maximum bladder storage during the night but moderately with nocturnal polyuria [10]. Currently nocturnal polyuria is classified as >33% of total urine production occurring overnight, >90 mL urine production/h of sleep or ≥130% of maximum voided volume by day. Whichever definition is used, accuracy relies on patient measurement and recording. The integration of TANGO findings and bladder diary data may suggest multiple causal pathways for nocturnal urine overproduction that warrant exploration. Such underlying causes have been sub-classified into global polyuria (e.g. diabetes or polydipsia) or nocturnal polyuria (e.g. congestive cardiac failure, sleep disordered breathing, peripheral oedema) [11]. Of the causes of nocturia related to a decreased night time bladder capacity suggested by Weiss [11], TANGO captures all except calculi and prostatic enlargement. Clinical judgement mandated the inclusion of kidney disease,

peripheral oedema, unstable diabetes mellitus, hypertension, and postural hypotension in TANGO. These items did not necessarily show the highest endorsement levels or strongest univariate regression with nocturia frequency but could all lie on a direct causal pathway with nocturia.

Unfragmented sleep of 7–8 h is required to maintain wellbeing [12]. Nocturia and worry are the most common causes of sleep disturbance, being implicated in both sleep onset and maintenance dysfunction [13]. TANGO distils the discriminating items related to insomnia, sleep quality and sleep disordered breathing and interprets the most clinically relevant aspects of each of these symptoms. Our analysis has shown that the following sleep variables are pertinent in patients with nocturia: sleep quality that an individual would describe as 'very bad', sleep latency of ≥30 min, and ≤5 h of total sleep at night.

The frequency of nocturia significantly increases with the severity of sleep disordered breathing [14]. Sleep apnoea involves recurrent upper airway obstruction that induces acute and chronic haemodynamic effects. During the obstructive phase negative intrathoracic pressures increase myocardial oxygen consumption and change ventricular load. Arterial blood pressure rises at the end of the apnoea episode with repetitive bradycardia, followed by tachycardia episodes during subsequent sleep. Over time patients can develop systemic hypertension, inflammation and atherosclerosis. The beneficial impact of positive pressure ventilation on respiratory patterns in people with sleep apnoea is well known; however, treatment also decreases nocturnal urine volume and urine electrolyte contents, ultimately improving nocturia frequency [15]. TANGO captures the indicators and comorbidities of sleep disordered breathing.

To facilitate the identification of LUTS of clinical relevance to nocturia, and to ensure TANGO is useful outside the specialty of continence, five validated and discriminating bladder items have been included. As would be expected the items retained identify presentation of an overactive bladder and prostatic obstruction to voiding. Consistent with previous reports [16], analysis of our data indicated the median time to first nocturia episode to be 3 h and confirmed a highly significant relationship between this interval and frequency of nocturia. TANGO includes the item 'I need to get up to pass urine within 3 h of going to sleep' to flag a likely mismatch between urine production and bladder storage.

Mental health and aspects of wellbeing impact on sleep and may induce wakefulness or early waking, known hallmarks of insomnia. Holistic management of nocturia must include an understanding of issues that impact an individual's ability to relax at night and maintain sleep. To identify obvious anxiety or depression the TANGO-LF included the entire Hospital Anxiety and Depression Scale (HADS). Analysis summed the two domains separately and also scrutinised individual items. Analysis showed that the HADS anxiety domain score was not related to nocturia frequency. This is in agreement with a previous report of an unclear association between anxiety and nocturia [17].

Depression has a more robust association with nocturia, findings mirrored in the TANGO-LF data, where four of the HADS depression sub-scale items were significantly associated with high frequency of nocturia and also highly endorsed. The TANGO-SF includes one of these items, the decision based on corrected item correlation. Layout of the tool facilitates visual screening for connected issues e.g. sleep latency.

Health status, daytime sleepiness, and falls history complete the wellbeing domain of TANGO. Nocturnal voiding is known to cause fragmented sleep, fatigue and impaired daytime function [12]. These extreme effects are reflected in the fact that even moderate sleep deprivation is at least as dangerous when driving as alcohol intoxication [18]. Dizziness and a higher risk of falls have a clear association with nocturia and have been included in the TANGO tool to prompt clinicians to search for causes of postural hypotension, vestibular disorders, poor balance or impaired mobility. Each of these variables increases the risk of mortality and is on the direct causal pathway of nocturia, warranting identification and investigation.

Future work will extend the psychometric testing of TANGO. As the TANGO-LF was not administered to a control group, community-dwelling participants along with individuals free of nocturia will be included in validation studies. Each of the TANGO items will be validated against bladder diary measures, smart device data capture, medical records, and a LUTS-specific quality-of-life measure. The responsiveness of TANGO to capture patient outcomes after intervention will also be tested.

Our earlier work has shown the greatest risks attached to frequent nocturia appear to be where dysfunctions coexist. TANGO clearly highlights multiple and co-existing disorders in patients with nocturia. The metric has been designed for completion by individuals who wake more than once each night, as this is the population that show the highest morbidity and are most at risk of adverse events. TANGO was developed across a wide age group and is therefore generalisable to adults from midlife onwards. Future work will establish any differences in the older cohort in residential care and ascertain test re-test reliability. Furthermore, the development of an accompanying clinical pathway for each flagged TANGO item may assist clinicians in bundling care interventions and evaluating efficacy of therapy.

Conclusion

The present study has addressed the gap between nocturia arising from multiple aetiologies and the symptom being

evaluated as a part of the overactive bladder. A novel patient-completed, multidisciplinary screening metric has been developed to allow capture of multiple and co-existing variables that may be co-contributing to nocturia. By assisting clinicians to tailor intervention to more than one causal factor of nocturia simultaneously, the patient outcome for this symptom that currently shows only a modest reduction after monotherapy may be improved.

Acknowledgements

The research time of Wendy F. Bower has been supported by grants from both The Australian Bladder Foundation and Ferring Pharmaceuticals Australia.

Conflicts of Interest

Wendy F. Bower reports grants from Ferring Pharmaceuticals, during the conduct of the study.

References

1 **Bower W, Whishaw DM, Khan F.** Nocturia as a marker of poor health: causal associations to inform care. *Neurourol Urodyn* 2016; [Epub ahead of print]. doi: 10.1002/nau.23000

2 **Obayashi K, Saeki K, Kurumatani N.** Association between melatonin secretion and nocturia in elderly individuals: a cross-sectional study of the HEIJO-KYO cohort. *J Urol* 2014; 191: 1816–21

3 **Drake MJ.** Should nocturia not be called a lower urinary tract symptom? *Eur Urol* 2015; 67: 289–90

4 **Gulur DM, Mevcha AM, Drake MJ.** Nocturia as a manifestation of systemic disease. *BJU Int* 2011; 107: 702–13

5 **Nimeh T, Alvarez P, Mufarreh N, Lerner L.** Nocturia: current evaluation and treatment for urology. *Curr Urol Rep* 2015; 16: 66

6 **Oelke M, Adler E, Marschall-Kehrel D, Herrmann TR, Berges R.** Nocturia: state of the art and critical analysis of current assessment and treatment strategies. *World J Urol* 2014; 32: 1109–17

7 **Rosen R, Holm-Larsen T, Kupelian V, Wein AJ.** Consequences of nocturia. *Postgrad Med* 2013; 125: 38–46

8 **Booth J, Lawrence M, O'Neill K, McMillan L.** Exploring older peoples' experiences of nocturia: a poorly recognised urinary condition that limits participation. *Disabil Rehabil* 2010; 32: 765–74

9 **Bower WFEC, Whishaw DM, Khan F.** Development of a long-form screening tool for identifying clinically relevant co-morbidities of nocturia. *Aust N Z Continence J* 2016; 22: 40–7

10 **Avulova S, Blanker MH, van Doorn B et al.** Determinants of nocturia severity in men, derived from frequency-volume charts. *Scand J Urol* 2015; 49: 185–8

11 **Weiss JP.** Nocturia:"do the math". *J Urol* 2006; 175: S16–8

12 **Temml C, Ponholzer A, Gujahr G, Berger I, Marszalek M, Madersbacher S.** Nocturia is an age-independent risk factor for hip fractures in men. *Neurourol Urodyn* 2009; 28: 949–52

13 **Brunner A, Riss P.** Nocturia in women. *Maturitas* 2011; 70: 16–21

14 **Ayik S, Bal K, Akhan G.** The association of nocturia with sleep disorders and metabolic and chronic pulmonary conditions: data derived from the polysomnographic evaluations of 730 patients. *Turk J Med Sci* 2014; 44: 249–54

15 **Miyauchi Y, Okazoe H, Okujyo M et al.** Effect of the continuous positive airway pressure on the nocturnal urine volume or night-time frequency in patients with obstructive sleep apnea syndrome. *Urology* 2015; 85: 333–6

16 **Bliwise DL, Holm-Larsen T, Goble S, Nørgaard JP.** Short time to first void is associated with lower whole-night sleep quality in nocturia patients. *J Clin Sleep Med* 2015; 11: 53–5

17 **Breyer BN, Shindel AW, Erickson BA, Blaschko SD, Steers WD, Rosen RC.** The association of depression, anxiety and nocturia: a systematic review. *J Urol* 2013; 190: 953–7

18 **Van Kerrebroeck P.** Nocturia: current status and future perspectives. *Curr Opin Obstet Gynecol* 2011; 23: 376–85

19 **Australian Bureau of Statistics (ABS).** *Socioeconomic Indexes for Areas (SEIFA), Australia, 2011, 'Table 2: Postal Area (POA) Index of Relative Socio-economic Advantage & Disadvantage, 2011' data cube: Excel spreadsheet, cat. no.2033.0.55.001. 2011. Available at: http://www.abs.gov.au/ausstats/abs@.nsf/DetailsPage/2033.0.55.0012011?OpenDocument. Accessed 12 April 2016.*

Appendix 1

TANGO-SF screening questionnaire

Place a tick ☑ next to each statement which is TRUE/ CORRECT for you.

☐	My ankles, feet or legs swell during the day.	CARDIO / METABOLIC
☐	I take fluid tablets (e.g. Lasix).	
☐	I have kidney disease.	
☐	I take tablets to control my blood pressure.	
☐	I often get dizzy when standing up.	
☐	I have high blood sugar OR diabetes.	
☐	My blood sugar levels are difficult to keep stable.	
☐	I have 5 hours or less sleep per night.	SLEEP
☐	I would describe my sleep quality as *bad*.	
☐	It takes me longer than 30 minutes to fall asleep at night.	
☐	I have difficulty staying asleep at night because of my bladder.	
☐	I often experience pain at night.	
☐	I have been told I snore loudly OR stop breathing at night.	
☐	I need to get up to pass urine within 3 hours of going to sleep.	URINARY TRACT
☐	I experience a sudden urge to urinate on most days.	
☐	I have a bladder urgency accident once a week or more.	
☐	I often need to strain or push to start urinating.	
☐	I have an enlarged prostate gland.(MALES ONLY)	
☐	In general, I would say that my health is *not good*.	WELLBEING
☐	I have trouble staying awake while driving, eating or during social activities.	
☐	I have had a fall in the last 3 months.	
☐	I don't look forward to things with as much enjoyment as I used to.	

Correspondence: Wendy F. Bower, Royal Melbourne Hospital, Royal Park Campus, 34-54 Poplar Road, Parkville, Victoria 3052, Australia.

e-mail: wendy.bower@mh.org.au

Abbreviations: HADS, Hospital Anxiety and Depression Scale; LF, Long-Form; SF, Short-Form; TANGO, Targeting the individual's Aetiology of Nocturia to Guide Outcomes.

TANGO NOCTURIA SCREEN

	Place an 'X' beside each statement to indicate whether or not it is true for you.	True	False
CARDIO / METABOLIC	My ankles, feet or legs swell during the day.		
	I take fluid tablets (e.g. Lasix).		
	I have kidney disease.		
	I take tablets to control my blood pressure.		
	I often get dizzy when standing up.		
	I have high blood sugar OR diabetes.		
	My blood sugar levels are difficult to keep stable.		
SLEEP	I have 5 hours or less sleep per night.		
	I would describe my sleep quality as *bad*.		
	It takes me longer than 30 minutes to fall asleep at night.		
	I have difficulty staying asleep at night because of my bladder.		
	I often experience pain at night.		
	I have been told I snore loudly OR stop breathing at night.		
URINARY TRACT	I need to get up to pass urine within 3 hours of going to sleep.		
	I experience a sudden urge to urinate on most days.		
	I have a bladder urgency accident once a week or more.		
	I often need to strain or push to start urinating.		
	I have an enlarged prostate gland. (MALES ONLY)		
WELLBEING	In general, I would say that my health is *not good*.		
	I have trouble staying awake while driving, eating or during social activities.		
	I have had a fall in the last 3 months.		
	I don't look forward to things with as much enjoyment as I used to.		

Number of times you wake up to urinate during the night? _____

Bower WF, Rose GE, Ervin CF, Goldin J, Whishaw DM, Khan F. TANGO - a screening tool to identify comorbidities on the causal pathway of Nocturia. BJU Int. 2017 Jan 11. doi: 10.1111/bju.13774.