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Etiology of nocturia response in men with diminished bladder capacity

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Aims: To test the hypothesis that patients with nocturia owing to diminished global or nocturnal bladder capacity improve via increased bladder capacity.

Methods: This is a retrospective analysis of voiding diaries completed at a VA urology clinic between 2008–2017. Inclusion required patients aged at least 18 years, male, undergoing treatment for nocturia, and having completed at least two 24-hour voiding diaries ≥1 month apart. Patients were divided into two cohorts: responders (any decline in nocturia) and non-responders (no change or any increase in nocturia). Patients were further sub-stratified as having low global bladder capacity (maximum voided volume [MVV] <200 mL) versus low nocturnal bladder capacity (nocturnal maximum voided volume [NMVV] <200 mL and MVV ≥200 mL). Wilcoxon rank-sum was applied with a Bonferroni correction to test significance.

Results: Forty pre- and post-treatment diaries from 27 patients, and 19 pre- and post-treatment diaries from 17 patients were identified as having low global and low nocturnal bladder capacity, respectively. Nocturia responders with low global bladder capacity demonstrated significant decline compared to non-responders in nocturnal urine volume (NUV) (−140 vs +75, $P < 0.01$) and nocturnal bladder capacity index (NBCi) (−0.59 vs +0.23, $P < 0.01$). Patients with low nocturnal bladder capacity similarly demonstrated decreased NUV (−30 vs +160, $P = 0.04$) and NBCi (−1.4 vs +0.33, $P < 0.01$). There was no significant change in MVV or NMVV for either group.

Conclusions: Treatment directed at lowering nocturnal urine production and enabling patients to consistently void at capacity is a rational strategy to treat nocturia in patients with low bladder capacity.

KEYWORDS
nocturia, LUTS

1 | INTRODUCTION

Nocturia, defined as voiding that occurs during the hours of intended sleep, is among the most common urological conditions in the general population.[1] Older patients are particularly affected, with an estimated 56% of males aged 75 years or older reporting symptoms of nocturia in the National Health and Nutrition Examination Survey (NHANES).[2] Several studies have demonstrated nocturia to be associated with both increased mortality and a lower quality of life.[3–5]

The cause of nocturia is often complex, and management is predicated on identifying the specific mechanism

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underlying a patient's symptoms. One cause of nocturia is diminished bladder capacity, which may be present throughout the day (global), or only during the hours of intended sleep (nocturnal).[6] In either case, nocturnal voiding is driven by nocturnal urine volume in excess of nocturnal urine storage capacity.[6] Diminished bladder capacity among older men has many urological causes, among the most common being prostatic obstruction, which results in a weaker urinary flow and thus poor bladder emptying.[7]

Management of nocturia owing to low capacity bladder may include behavioral techniques such as restricted fluid intake, bladder training, urge suppression, and pelvic floor exercises; pharmacotherapy with α-adrenergic antagonists, antimuscarinics, or β3-adrenergic agonists; or more invasive interventions, such as trans-urethral resection of the prostate (TURP), neuromodulation or botulinum toxin detrusor muscle injections.[8–10]

Although the urologist's toolkit continues to expand, clinical drug trials have shown statistically significant—but clinically equivocal—outcomes, and real-world observational studies have likewise demonstrated poor efficacy of treatment directed at nocturia owing to diminished bladder capacity.[11–15] As such, an effective standard management strategy for the treatment of nocturia due to low capacity bladder has yet to be identified.

The 24-hour voiding diary is a valuable resource in the clinical evaluation of nocturia.[6] Diary analysis can be used initially for diagnosis of nocturia owing to small capacity bladders, subsequently to evaluate a patient's response to treatment. and to provide patients with feedback to reinforce behaviors that lead to improvement in nocturia severity. The overall aim of this responder analysis study is to identify mechanisms that underlie nocturia improvement in men with a small capacity bladder. Specifically, we seek to test the hypothesis that patients whose nocturia is primarily due to small capacity bladder improve as a result of increased bladder capacity.

2 | MATERIALS AND METHODS

2.1 | Patients

A database of 749 voiding diaries completed by 425 patients from a Veterans Affairs-based urology clinic seeking treatment for lower urinary tract symptoms (LUTS) was retrospectively analyzed. Included were male patients aged 18 years or older who had a baseline voiding diary showing at least 1 nocturic episode and completed a follow-up diary 30 or more days after the baseline diary. Voiding diaries with incomplete data were not included. Of the initial set, 466 voiding diaries from 124 patients met the inclusion criteria. Table 1 provides an overview of patient demographics, including age, race, comorbidities, baseline α-adrenergic blocker status, urological surgery history, and radiation

TABLE 1 Baseline characteristics of patients with low capacity bladder

	Low global bladder capacity		Low nocturnal bladder capacity	
	Responder ($n = 11$)	Non-responder ($n = 16$)	Responder ($n = 7$)	Non-responder ($n = 10$)
Age	67 (52-82)	70 (60-80)	74 (68-81)	72 (53-91)
Ethnicity				
Caucasian	4 (36.4)	5 (31.2)	2 (28.6)	6 (60)
African-American	6 (54.5)	9 (56.2)	4 (57.1)	2 (20)
Other/unknown	1 (9.1)	2 (12.5)	1 (14.3)	2 (20)
Comorbidities				
Hypertension	7 (63.6)	11 (68.8)	4 (57.1)	7 (70)
Diabetes	0 (0)	2 (12.5)	2 (28.6)	0 (0)
Sleep apnea	2 (18.2)	1 (6.2)	1 (14.3)	0 (0)
Medication				
α-blocker	9 (81.8)	10 (62.5)	4 (57.1)	8 (80)
Surgery				
RRP	0 (0)	0 (0)	0 (0)	0 (0)
TURP	0 (0.0)	1 (6.2)	2 (28.6)	1 (10)
Urethroplasty	1 (9.1)	0 (0)	0 (0)	0 (0)
Radiation				
EBRT	1 (9.1)	0 (0)	0 (0)	0 (0)
Brachytherapy	0 (0)	1 (6.2)	0 (0)	0 (0)

history. For demographic data, categorical variables are reported as frequency (proportion), and continuous variables are reported as median (interquartile range).

2.2 | Study design and procedures

Data for this study were obtained from a real-world setting, whereby patients seeking treatment at a urology clinic were asked to complete paper voiding diaries as per best practice standards in the diagnosis and evaluation of LUTS.[10] Patients were managed according to the framework depicted in Figure 1. Initially, patients were managed with behavioral advice (drinking fluids only as needed for thirst and/or bladder training), and, if warranted, with pharmacological treatment utilizing anticholinergics or β3 agonists for urgency/overactive bladder; α-blockers and/or 5-α-reductase inhibitors for prostatic obstruction; and outlet reducing surgery for urinary retention refractory to pharmacologic treatment. Only a single intervention (ie, start of new medication or change of dose) was implemented at each visit to effectively assess response to treatment. This study was not powered to determine a treatment effect for a specific treatment, but rather to investigate the physiological mechanisms relating to how patients saw improvement.

Patients were divided into two cohorts: responders (178 diaries [89 pre- and post-treatment] from 55 patients), defined as a decline of at least one nocturic episode between two subsequent diaries, and non-responders (288 diaries [144 pre- and post-treatment] from 69 patients), defined as having no change or an increase in nocturia between two subsequent diaries. Patients were further sub-stratified as having low global bladder capacity (maximum voided volume [MVV] <200 mL) versus low nocturnal bladder capacity, (nocturnal maximum voided volume [NMVV] <200 mL and MVV ≥200 mL). There is no standard definition of low capacity bladder from voiding diaries, so a cut-off of 200 mL was chosen for MVV and NMVV

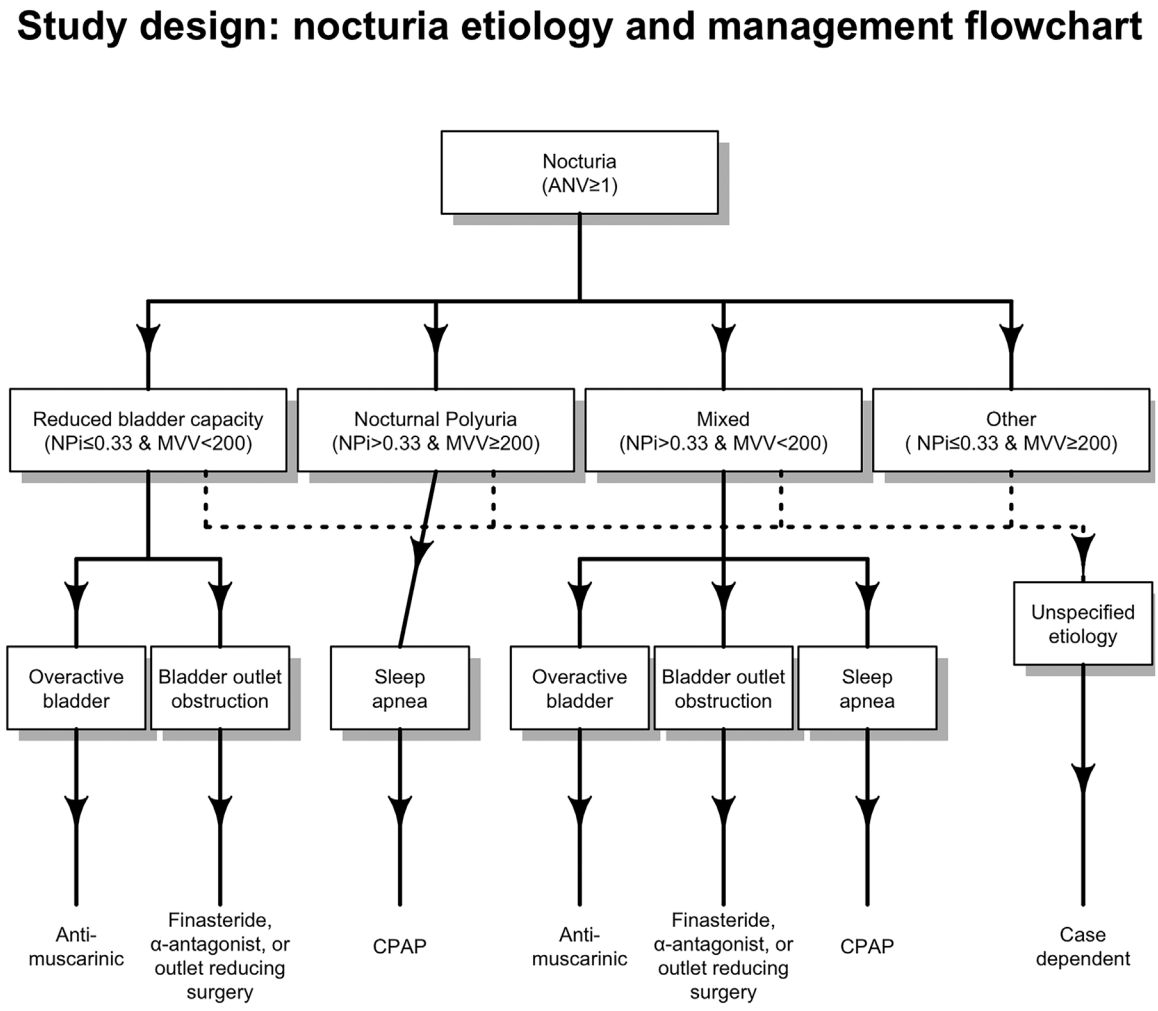

FIGURE 1 Flow chart of study design. Row 1 begins with a patient with nocturia defined by ANV ≥ 1. Row 2 divided patients by diary information, where maximum voided volume (MVV) < 200 indicates reduced bladder capacity, and nocturnal polyuria index (NPi) > 0.33 indicates nocturnal polyuria. Row 3 further subdivides theetiology into treatable conditions. Row 4 demonstrates the treatment used for nocturia etiologies

because this approximates the lower standard deviation of MVV in populations studied with conditions predisposing them to low bladder capacity, and is below lower capacities observed in asymptomatic patients.[16–17]

Diary parameters that were calculated from the voiding diaries were: 24-hour urine volume, calculated as total volume of urine produced during a 24-hour period; nocturnal urine volume (NUV), calculated as total volume of urine passed during the night, including the first morning void; maximum voided volume (MVV), calculated as the largest single voided volume in a 24-hour period; nocturnal maximum voided volume (NMVV), calculated as the largest single voided volume during the night; actual number of nighty voids (ANV), defined as the number of voids recorded from the time the individual goes to bed with intention of sleeping, to the time the individual wakes with the intention of rising; nocturia index (Ni), calculated as $Ni = NUV/MVV$ (when $Ni > 1$, NUV exceeds maximum storage capacity and nocturia or enuresis occurs); nocturnal polyuria index (NPi), calculated as NPi = NUV/(24-hour urine volume); nocturnal urine production (NUP), calculated as NUP = NUV/(# hours asleep); predicted number of nightly voids (PNV), calculated as $PNV = Ni-1$; nocturnal bladder capacity index (NBCi), calculated as ANV−PNV ($NBCi > 0$ indicates that nocturia will occur at voided volumes < MVV. $NBCi > 2$ associated with severe nocturia); first uninterrupted sleep period (FUSP), calculated as # hours between the time the individual goes to bed with the intention of sleeping to the time of first awakening.

2.3 | Statistical analysis

Baseline and change from baseline values (difference between post- and pre-treatment voiding diaries) were calculated for all diary parameters. These values were reported for both responders and non-responders, in both the low global bladder capacity and low nocturnal bladder capacity cohort. Diary parameters are reported as median (95% confidence interval) using Wilcoxon confidence interval estimates. Continuous and categorical parameters were compared using unpaired Wilcoxon rank-sum tests and the chi-square tests, respectively; Bonferroni correction was applied for multiple comparisons. Univariate linear regression was performed on pre- to post-treatment change in nocturia severity (ANV) and the change in all aforementioned voiding diary parameters.

3 | RESULTS

Of the original cohort, 59 baseline diaries from 44 patients met criteria for either low global or nocturnal capacity bladder, representing 25% of the original cohort of diaries (35% of patients). In the low global bladder capacity cohort, 40 diaries were completed at the pre-treatment (baseline) visit, and 40 were completed at the post-treatment visit. In the low nocturnal bladder capacity cohort, 19 diaries were completed at the pre-treatment (baseline) visit, and 19 were completed at the post-treatment visit. Baseline voiding parameters in responders were compared to non-responders; low global bladder capacity demonstrated a large difference in ANV (4 vs 2, respectively; $P = 0.011$). Slightly more than half of the cohort with low global bladder capacity also had nocturnal polyuria ($NPi > 0.33$) at baseline (22 diaries, 55%). Five patients (26%) with low nocturnal bladder capacity had nocturnal polyuria at baseline. No differences were seen in baseline voiding parameters in responders compared to non-responders in patients with low nocturnal bladder capacity. An overview of these results is provided in Table 2.

TABLE 2 Baseline voiding diary parameters for responders versus non-responders with low global or low nocturnal bladder capacity

	Low global bladder capacity			Low nocturnal bladder capacity		
	Responder ($n = 13$)	**Non-responder ($n = 27$)**	***P*-val**	**Responder ($n = 7$)**	**Non-responder ($n = 12$)**	***P*-val**
24 h volume	1100 (870-1500)	1100 (1000-1300)	1	1300 (1200-2000)	1400 (1300-1800)	1
Voids in 24 h	12 (10-15)	12 (10-13)	1	10 (9-13)	10 (9-12)	1
ANV	4 (3-5)	2 (2-3)	0.011	2 (1.5-4)	1.5 (1-2.5)	1
MVV	150 (120-180)	180 (140-170)	1	240 (220-350)	230 (210-320)	1
NBCi	1.3 (1-3)	0.64 (0.65-1.2)	0.19	1.7 (1.1-2.9)	1.1 (0.78-1.4)	0.69
Ni	3.1 (2.4-4.3)	2.5 (2.2-2.8)	1	1.2 (0.75-2.7)	1.6 (1.2-2.2)	1
NMVV	150 (92-160)	150 (120-160)	1	180 (150-180)	140 (120-170)	1
NPi	0.38 (0.31-0.55)	0.33 (0.3-0.38)	1	0.22 (0.18-0.43)	0.27 (0.21-0.35)	1
NUP	64 (47-78)	47 (42-56)	1	49 (27-69)	50 (43-70)	1
NUV	540 (350-690)	380 (330-440)	1	420 (220-580)	410 (320-540)	1

Low global bladder capacity = MVV < 200 mL; Low nocturnal bladder capacity = NMVV < 200 mL; and MVV ≥ 200 mL. ANV, actual nocturnal voids; MVV, maximum voided volume; NBCi, nocturnal bladder capacity index; Ni, nocturia index; NMVV, nocturnal maximum voided volume; NPi, nocturnal polyuria index; NUP, nocturnal urine production; NUV, nocturnal urine volume.

Patient characteristics were compared between patients in the low global bladder capacity group and those with the low nocturnal bladder capacity, which included age (68 vs 74 years, respectively), ethnicity (33 vs 47% white; 56 vs 35% African-American), comorbidities (67 vs 65% hypertension, 7 vs 12% diabetes mellitus, 11 vs 6% sleep apnea), baseline α-blocker status (70 vs 71%), urologic surgery (0 vs 0 radical retropubic prostatectomy, 4 vs 18% transurethral resection of prostate, 4 vs 0% urethroplasty), and radiation (4 vs 0% external beam radiation therapy, 4 vs 0% brachytherapy). Further breakdown of demographics in cohorts between responders and non-responders is reported in Table 1.

The change in patients with low global bladder capacity from baseline in responders compared with non-responders, respectively, revealed significant differences in NBCi (−0.59 vs +0.23; $P < 0.01$), Ni (−1.1 vs +0.24; $P < 0.01$), NPi (−0.082 vs +0.048; $P < 0.01$), NUP (−8.4 vs +10 mL/h; $P = 0.02$) and NUV (−140 vs +75 mL; $P < 0.01$). Significant differences were seen in the change from baseline among patients with low nocturnal bladder capacity in NUV (−30 vs +160 mL; $P = 0.04$) and NBCi (−1.4 vs +0.33; $P < 0.01$) in responders compared to non-responders, respectively. These results are further detailed in Table 3.

To quantify the effects of these relationships, a univariate linear regression was performed on the different voiding diary parameters as a function of change in nocturia severity (Table 4). Notably, MVV, and NMVV had no significant relationship in patients with either low global or low nocturnal bladder capacity. Additionally, the regression between ANV and 24 h was found to be significant for patients with low nocturnal bladder capacity (slope coefficient = 1.6E3; $P < 0.001$), but not significant in patients with low global bladder capacity (slope coefficient = 2.8E5; $P = 0.9$).

4 | DISCUSSION

To date, few investigations have utilized voiding diaries to examine the mechanism of treatment response. Therefore, this examination of the mechanisms by which patients with a low capacity bladder respond to nocturia treatment reflects a novel investigative utility of voiding diaries. Patients with low global bladder capacity achieved relief of their nocturia symptoms through four mechanisms:

1). *Patients who responded tended to drink less*. This is reflected in decreased 24-hour urine volume. Fluid restriction is already an accepted method of achieving improvement in nocturia severity; this study provides additional evidence to seek means to diminish nocturnal urine output in patients with low capacity bladders—whether or not nocturnal polyuria is present.[11,18] Notably, fluid restriction should be implemented safely in patients more susceptible to dehydration, and particular care must be taken when treating the elderly, who have a decreased thirst response to dehydration and can less reliably self-regulate hydration.[19–21] Lowering nocturnal urine production is a rational strategy to treat nocturia in patients with low bladder capacity despite the absence of nocturnal polyuria.

2). *Patients who improved had diminished nocturnal urine production compared to their pre-treatment visit* (reflected in decreased NUV and NUP). This indicates that

TABLE 3 Change from baseline voiding diary parameters for responders versus non-responders with low global or low nocturnal bladder capacity

	Low global bladder capacity			Low nocturnal bladder capacity		
	Responder ($n = 13$)	Non-responder ($n = 27$)	*P*-val	Responder ($n = 7$)	Non-responder ($n = 12$)	*P*-val
24 h volume	−130 (−460-45)	66 (−85-180)	0.72	−120 (−400-72)	75 (25-300)	0.11
Voids in 24 h	−2 (−3.5-−1)	0 (−1-1)	0.059	−1 (−3.5-7.8e-05)	1 (4.5e-05-2)	0.084
ANV	−2 (−2.5-−1.5)	0 (1-2)	<0.01	−1 (−2-−1)	1 (1-2.5)	<0.01
MVV	0 (−38-41)	−2.5 (−25-29)	1	0 (−60-65)	7.5 (−7.5-48)	1
NBCi	−0.59 (−1.4-−0.3)	0.23 (0.093-0.57)	<0.01	−1.4 (−1.6-−0.82)	0.33 (0.16-0.73)	<0.01
Ni	−1.1 (−1.4-−0.69)	0.24 (0.11-0.63)	<0.01	−0.24 (−0.95-0.12)	0.37 (0.15-0.83)	0.055
NMVV	−7.5 (−70-45)	0 (−20-32)	1	0 (−140-73)	40 (5e-05-75)	1
NPi	−0.082 (−0.14-−0.043)	0.048 (0.0056-0.083)	<0.01	−0.045 (−0.087-0.051)	0.039 (0.0063-0.1)	0.92
NUP	−8.4 (−31-1.5)	10 (3-20)	0.02	−8.5 (−34-17)	17 (8.2-29)	0.25
NUV	−140 (−290-75)	75 (35-160)	<0.01	−30 (−230-65)	160 (75-250)	0.04

Low global bladder capacity = MVV < 200 mL; Low nocturnal bladder capacity = NMVV < 200 mL; and MVV ≥ 200 mL. ANV, actual nocturnal voids; MVV, maximum voided volume; NBCi, nocturnal bladder capacity index; Ni, nocturia index; NMVV, nocturnal maximum voided volume; NPi, nocturnal polyuria index; NUP, nocturnal urine production; NUV, nocturnal urine volume.

TABLE 4 Univariate linear regression of change in nocturia severity and change in voiding diary parameters

	Low global capacity ($n = 40$)		Low nocturnal capacity ($n = 19$)	
	Slope coefficient	***P*-val**	**Slope coefficient**	***P*-val**
24 h volume	2.8E5 (−2.0E4-2.6E4)	0.9	1.6E3 (1.2E3-2.0E3)	<0.001
Voids in 24 h	0.17 (0.098-0.24)	0.022	0.3 (0.24-0.36)	<0.001
MVV	−1.5E3 (−3.5E3-5.0E4)	0.44	−2.6E3 (−5.2E3-0.0)	0.33
NBCi	0.95 (0.81-1.09)	<0.001	1.1 (0.97-1.2)	<0.001
Ni	0.96 (0.86-1.06)	<0.001	1.1 (0.96-1.24)	<0.001
NMVV	−3.2E4 (−2.6E3-2.0E3)	0.89	2.5E3 (8.0E4-4.2E3)	0.14
NPi	7.0 (5.8-8.2)	<0.001	4.6 (3.2-6.0)	0.0018
NUP	0.026 (0.020-0.032)	<0.001	0.026 (0.020-0.032)	<0.001
NUV	3.6E3 (3.0E3-4.2E3)	<0.001	4.0E3 (3.3E3-4.5E3)	<0.001

Low global bladder capacity = MVV < 200 mL; Low nocturnal bladder capacity = NMVV < 200 mL; and MVV ≥ 200 mL. ANV, actual nocturnal voids; MVV, maximum voided volume; NBCi, nocturnal bladder capacity index; Ni, nocturia index; NMVV, nocturnal maximum voided volume; NPi, nocturnal polyuria index; NUP, nocturnal urine production; NUV, nocturnal urine volume.

patients were producing less urine at night, which can be explained by a decrease in nocturnal fluid intake, or through reduced natriuresis or greater free water reabsorption (as might be mediated by arginine vasopressin).

3). *Responders experienced closer alignment of nocturnal urine volume with bladder capacity* (reflected in decreased Ni). This is likely due mainly to decreased nocturnal urine volume, as maximum voided volume did not change.

4). *Responders experienced no increase in bladder capacity compared to non-responders, but rather had an increased tendency for nocturia voids to occur at volumes close to their bladder capacity* (reflected in decreased NBCi). This was perhaps the most striking finding of our analysis, as it refutes the notion that nocturia improvement in patients with underlying low bladder capacity comes about via increased voided volumes.

Taken together, positive response to nocturia treatment appears to be mediated by closer alignment of nocturnal voided volume and bladder capacity, as well as by minimization of fluid intake and diminished nocturnal urine volume.

The regression analysis between ANV and low global and nocturnal bladder capacity reveals that a decrease in 24 h volume was associated with lower ANV in patients with low nocturnal bladder capacity, but not in low global bladder capacity. Whether decreased intake (and hence output) in patients with low nocturnal (but normal global) capacity is more effective in reducing nocturia severity than in patients with low global capacity is an interesting observation which warrants further investigation.

Despite the observation that global or nocturnal bladder capacities were not significantly changed in patients whose nocturia improved, treatment designed to promote voiding at capacity results in improved nocturia in men with low bladder capacity. Behavioral techniques such as bladder training, pelvic floor exercises, and urge suppression were devised to allow patients to void closer to capacity, and thus are likely options for the management of patients with low capacity bladders.[22,23] In order to realize the greatest benefit in control of nocturia, even in patients requiring treatment for urgency and/or prostatic obstruction should be encouraged to try to void at capacity and diminish nocturnal urine output through an individualized treatment plan.

Unfortunately, current pharmacologic treatment options for nocturia due to small capacity bladder are less than encouraging. Burgio et al[22] demonstrated that patients already prescribed α-blockers who were given behavioral advice and trained on behavioral techniques had a greater drop in nocturia severity compared to patients prescribed oxybutynin in the MOTIVE trial. Similar results were also seen with behavioral modifications compared with α-blockers,[23] demonstrating again that behavioral techniques were superior to pharmacological therapy. As there are currently no pharmacologic therapies available for increasing bladder capacity, there exists an urgent need to identify new strategies for increasing capacity.

There were no differences in baseline voiding parameters between responders and non-responders with low global bladder capacity, except for initial nocturia severity. This mirrors previous findings of greater nocturia severity at baseline in nocturia responders of all etiologies.[11] This finding conveys some potential implications in counseling patients bothered by nocturia. Patients with 3-4 voids per night are likely to see a greater improvement in symptoms and can thus be counseled more enthusiastically about potential improvement, whereas patients with one or two voids per night at their initial visit should have tempered expectations of

symptomatic resolution. On the other hand, patients with low nocturnal bladder capacity did not have worse nocturia severity at their initial visit and saw a lesser response when nocturia improved compared to patients with low global bladder capacity (−2 vs −1). Consequently, it appears improvement in this population cannot be predicted from their baseline voiding diaries.

Patient demographics incorporated in this study were: age, ethnicity, comorbidities, baseline α-blocker status, surgical history, and radiation history. The incidence of nocturia has been demonstrated to be different between certain races; specifically, blacks have been shown to have a higher incidence of nocturia than whites.[2] However, it has been determined that race is not a determining factor of nocturia severity, which is more related to the results from this study.[15] In contrast, existing studies have demonstrated that hypertension, diabetes mellitus, dyslipidemia, and obesity are associated with lower urinary tract symptoms in general, and more specifically, nocturia and benign prostatic hyperplasia.[24–26] Overactive bladder is weakly linked with obesity and diabetes mellitus.[27,28] Demographic results reported herein are not powered to draw definitive conclusions.

Limitations of this study include small sample size and possible errors in self-reported bladder volumes.[29] Single-day voiding diaries would appear to be less reliable than diaries spanning 3-5 days.[30] The participants of this study are all from a single VA institution treated by a single team, and the diaries are obtained, retrospectively. Different treatments were given according to the framework depicted in Figure 1, and as such, different treatments would likely determine the manner in which a patient improved (or did not improve). Patients were managed by a single treatment per visit in order to evaluate response to individual treatments; however, a multi-treatment approach at the initial visit may be a beneficial approach which was not addressed by this study. Some diary responses are taken from the same patient receiving a different treatment, and thus may add bias to the results.

5 | CONCLUSIONS

Patients with nocturia caused by low global bladder capacity had worse nocturia severity at baseline, and improved outcomes by decreasing nocturnal urine volume likely through both reduced fluid intake and voiding at volumes closer to capacity, even if increases in overall bladder capacity is not feasible. Whether methods of modifying nocturnal urine production through use of desmopressin, timed diuretics, continuous positive airway pressure (in sleep apnea patients), or antihypertensive medication for non-dipping nocturnal blood pressure remains to be seen and justify future investigative efforts.[31–37]

CONFLICT OF INTEREST

Dr Weiss reports personal fees from Ferring, personal fees from Pfizer, personal fees from Allergan, personal fees from Elsevier, personal fees from Astellas, outside the submitted work; Dr Epstein and Dr Monaghan have nothing to disclose.

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REFERENCES

1. van Kerrebroeck P, Abrams P, Chaikin D, et al. The standardisation of terminology in nocturia: report from the standardisation sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21:179–183.
2. Markland AD, Vaughan CP, Johnson TM, Goode PS, Redden DT, Burgio KL. Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey. *J Urol*. 2011;185:998–1002.
3. Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the third national health and nutrition examination survey. *J Urol*. 2011;185:571–577.
4. Lightner DJ, Krambeck AE, Jacobson DJ, et al. Nocturia is associated with an increased risk of coronary heart disease and death. *BJU Int*. 2012;110:848–853.
5. Tikkinen KA, Johnson TM, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. *Eur Urol*. 2010;57:488–498.
6. Marshall SD. Nocturia. *Campbell-Walsh Urology*. 11th ed. Philadelphia, PA: Elsevier; 2015. 1821–1835.
7. Garraway WM, Lee RJ, Collins GN. High prevalence of benign prostatic hypertrophy in the community. *Lancet*. 1991;338:469–471.
8. Leron E, Weintraub AY, Mastrolia SA, Schwarzman P. Overactive bladder syndrome: evaluation and management. *Curr Urol*. 2018;11:117–125.
9. Johnson TM, Markland AD, Goode PS, et al. Efficacy of adding behavioural treatment or antimuscarinic drug therapy to α-blocker therapy in men with nocturia. *BJU Int*. 2013;112:100–108.
10. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188:2455–2463.
11. Epstein M, Blaivas J, Wein AJ, Weiss JP. Nocturia treatment outcomes: analysis of contributory frequency volume chart parameters. *Neurourol Urodynam*. 2018;37:186–191.
12. Johnson TM, Burrows PK, Kusek JW, et al. The effect of doxazosin, finasteride and combination therapy on nocturia in men with benign prostatic hyperplasia. *J Urol*. 2007;178:2045–2051.
13. Yokoyama O, Yamaguchi O, Kakizaki H, et al. Efficacy of solifenacin on nocturia in Japanese patients with overactive bladder: impact on sleep evaluated by bladder diary. *J Urol*. 2011;186:170–174.
14. Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive

bladder: a head-to-head placebo-controlled trial. *BJU Int*. 2010; 105:58–66.
15. Nassau D, Avulova S, Friedman FM, Weiss JP, Blaivas JG. Prediction of nocturia severity in men: nocturnal urine overproduction vs race or metabolic risk factors. *JAMA Surg*. 2015;150: 125–128.
16. van Venrooij GE, Eckhardt MD, Boon TA. Data from frequency-volume charts versus maximum free flow rate, residual volume, and voiding cystometric estimated urethral obstruction grade and detrusor contractility grade in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. *Neurourol Urodyn*. 2002;21:450–456.
17. Mueller E, Latini J, Lux M, et al. Gender differences in 24-hour urinary diaries of asymptomatic North American adults. *J Urol*. 2005;173:490–492.
18. Tani M, Hirayama A, Torimoto K, Matsushita C, Yamada A, Fujimoto K. Guidance on water intake effectively improves urinary frequency in patients with nocturia. *Int J Urol*. 2014;21:595–600.
19. Stookey JD. High prevalence of plasma hypertonicity among community-dwelling older adults: results from NHANES III. *J Am Diet Assoc*. 2005;105:1231–1239.
20. Davies I, O'Neill PA, McLean KA, Catania J, Bennett D. Age-associated alterations in thirst and arginine vasopressin in response to a water or sodium load. *Age Ageing*. 1995;24:151–159.
21. Mack GW, Weseman CA, Langhans GW, Scherzer H, Gillen CM, Nadel ER. Body fluid balance in dehydrated healthy older men: thirst and renal osmoregulation. *J Appl Physiol*. 1994;76: 1615–1623.
22. Burgio KL, Goode PS, Johnson TM, et al. Behavioral versus drug treatment for overactive bladder in men: the Male Overactive Bladder Treatment in Veterans (MOTIVE) Trial. *J Am Geriatr Soc*. 2011;59:2209–2216.
23. Johnson TM, II, Vaughan CP, Goode PS, Bliwise DL, Markland AD, Huisingh C. Pilot results from a randomized trial in men comparing alpha-adrenergic antagonist versus behavior and exercise for nocturia and sleep. *Clin Ther*. 2016;38:2394–2406.
24. Hammarsten J, Högstedt B, Holthuis N, Mellström D. Components of the metabolic syndrome—Risk factors for the development of benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis*. 1998;1:157.
25. Parsons JK, Carter HB, Partin AW, et al. Metabolic factors associated with benign prostatic hyperplasia. *J Clin Endocrinol Metab*. 2006;91:2562–2568.
26. Rohrmann S, Smit E, Giovannucci E, Platz EA. Association between markers of the metabolic syndrome and lower urinary tract symptoms in the Third National Health and Nutrition Examination Survey (NHANES III). *Int J Obes (Lond)*. 2005;29:310–316.
27. Zacche MM, Giarenis I, Thiagamoorthy G, Robinson D, Cardozo L. Is there an association between aspects of the metabolic syndrome and overactive bladder? A prospective cohort study in women with lower urinary tract symptoms. *Eur J Obstet Gynecol Reprod Biol*. 2017;217:1–5.
28. Ikeda M, Nozawa K. Prevalence of overactive bladder and its related factors in Japanese patients with diabetes mellitus. *Endocr J*. 2015;62:847–854.
29. Hansen CP, Klarskov P. The accuracy of the frequency-volume chart: comparison of self-reported and measured volumes. *Br J Urol*. 1998;81:709–711.
30. van Haarst EP, Rudd Bosch JL. The optimal duration of frequency-volume charts related to compliance and reliability. *Neurourol Urodynam*. 2014;33:296–301.
31. Reynard JM, Cannon A, Yang Q, Abrams P. A novel therapy for nocturnal polyuria: a double-blind randomized trial of frusemide against placebo. *BJU Int*. 1998;81:215–218.
32. Fu FG, Lavery HJ, Wu DL. Reducing nocturia in the elderly: A randomized placebo-controlled trial of staggered furosemide and desmopressin. *Neurourol Urodynam*. 2011;30:312–316.
33. De Guchtenaere A, Vande Walle C, Van Sintjan P, et al. Desmopressin resistant nocturnal polyuria may benefit from furosemide therapy administered in the morning. *J Urol*. 2007; 178:2635–2639.
34. Friedman FM, Weiss JP. Desmopressin in the treatment of nocturia: clinical evidence and experience. *Ther Adv Urol*. 2013; 5:310–317.
35. Cohn JA, Kowalik CG, Reynolds WS, et al. Desmopressin acetate nasal spray for adults with nocturia. *Expert Rev Clin Pharmacol*. 2017;10:1281–1293.
36. Miyauchi Y, Okazoe H, Okujyo M, et al. Effect of the continuous positive airway pressure on the nocturnal urine volume or nighttime frequency in patients with obstructive sleep apnea syndrome. *J Urol*. 2015;85:333–336.
37. Feldstein CA. Nocturia in arterial hypertension: a prevalent, underreported, and sometimes underestimated association. *J Am Soc Hypertens*. 2013;7:75–84.

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