

Original Article

Steps toward identification of a novel cue-positive overactive bladder phenotype in women with high-bother urinary urgency

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Abstract: Objective: The objective of this study was to investigate the relationship between situational cues (running water, stress, cold, etc.) and overactive bladder (OAB) symptoms. Methods: Women scheduled for urodynamic studies for clinical indications completed surveys to characterize OAB (ICIQ-OAB and OAB-V3) and responses to situational cues (validated long-form cues survey and a novel short-form cues survey). Participants were divided into two groups (Low-Bother urgency vs. High-Bother urgency), and OAB and cue survey responses were compared. Results: A total of 47 participants were enrolled in the study with 36 meeting inclusion criteria (15 Low-Bother and 21 High-Bother) with an overall mean age of 60.0 ± 10.0 years. The High-Bother urgency group scored significantly higher on multiple cue items in the long-form ($P < 0.05$) and only "running water" in the short-form cues survey ($P < 0.05$). In addition, "running water" was the only cue that was scored higher in both surveys ($P < 0.05$). Conclusions: This study showed that patients with High-Bother urgency may have increased symptom responses to environmental, mood, and cognitive cues. These findings suggest increased sensitivity to cues, especially "running water" in participants with bothersome OAB and the potential presence of a cue-specific OAB phenotype.

Keywords: Overactive bladder, cues, lower urinary tract symptoms, urinary urge incontinence

Introduction

Overactive bladder (OAB) is defined by the International Continence Society as "urinary urgency, usually with urinary frequency and nocturia, with or without urgency urinary incontinence" [1]. OAB is highly prevalent and affects 16% of men and 33% of women over the age of 40 and 40% of men and 47% of women ≥ 65 years old in the United States [2, 3]. OAB symptoms are known to negatively impact quality of life including sexual satisfaction, mental health, and sleep quality [4, 5]. In addition, OAB is responsible for a large public health burden, and patients are subject to healthcare costs 2.5 times higher than those without OAB, increased ambulatory visits, and difficulty with treatment [6, 7].

Due to a lack of objective diagnostic tests for OAB, validated surveys are used to quantitate symptom severity and bother. Survey items measure the core OAB symptoms of frequency, urgency, nocturia, and urge incontinence and their associated bother [8-12]. However, while OAB is widespread, the impact on quality of life differs greatly among patients [4, 5], highlighting a pressing need to develop more distinct OAB phenotypes.

One particular area of interest in OAB phenotyping is the relationship between environmental, mood, and cognitive cues with OAB symptoms and bother [13]. Environmental cues include exposure to the sight of bathrooms, front doors, running water, or cold weather and are frequently described by patients. Mood cues

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include feelings of depression or increased tiredness. Cognitive cues include awareness of bathroom locations or thinking about voiding. Research suggests that certain cues may lead to increased activity in brain regions corresponding to attentional processes and bladder control [14]. In all cases, increased cue responsiveness implies that Pavlovian triggers may enforce stimulus-response loops which exacerbate OAB symptoms [13] and suggests that behavioral modification techniques or extinction therapy may represent effective treatment options in a subset of patients.

Patients with OAB may be more sensitive to cues than those without OAB [13, 15]. To further analyze this association, we developed a novel short form cues survey (**Appendix 1**). The goal of this study is to associate OAB symptom severity and bother to cue-responsivity to identify a potential cue-responsive OAB phenotype.

Methods

Participants

All components of this prospective study were approved by the institutional review board, and all participants signed informed consent prior to enrollment. Consecutive biological female participants of at least 21 years of age scheduled for clinically indicated urodynamics were approached. Demographics (age, sex, race/ethnicity), body mass index (BMI), and clinical history (medical history, medications, surgical history, urologic history) were recorded based on direct interviews and clinical chart review. Individuals with neurogenic lower urinary tract dysfunction as well as limited or absent bladder sensation were excluded.

Surveys

Four surveys were administered to participants prior to their urodynamics study as follows: 1) The International Consultation on Incontinence Questionnaire for Overactive Bladder (ICIQ-OAB) [8], which evaluates urinary frequency, nocturia, urinary urgency, and urge incontinence (0-4 scale) as well as impact on quality of life (0-10 scale) in each category, 2) The OAB Awareness tool (OAB-V3) (0-15 scale) in which higher scores correspond to increasing impact on quality of life [11, 12], and a score ≥ 4 indi-

cates “probable OAB” with high sensitivity and specificity [11], 3) A validated 37-item long-form urinary cues questionnaire designed to identify conditioned cues (environmental, mood, cognitive) associated with urinary urgency or urge incontinence in patients with OAB [13] (scored 1-5), and 4) A novel short-form cues survey with six items (three cues: cold weather, running water, feeling stressed/anxious and three neutral items: warm water, surfing the internet, being relaxed calm). All items were scored 0-4 using language consistent with the ICIQ-OAB. Both cue surveys included neutral/unlikely cues (i.e., warm water) to control for acquiescence bias where highly motivated subjects may choose the most positive responses regardless of content. For both surveys, an individual cue item score of ≥ 3 was considered a positive response.

Urodynamics

Urodynamics were performed according to International Continence Society Standards [16] using a Laborie XT Urodynamics system (Portsmouth, NH) with air-charged catheters at a standard initial fill rate of 40 ml/min. Rectal catheters were also placed for abdominal pressure recording. Results were determined by a fellowship-trained urogynecologist blinded to participant OAB status. Urodynamic data included detrusor overactivity, neurogenic voiding dysfunction, elevated post void residual, detrusor underactivity, decreased sensation, voiding dysfunction, stress urinary incontinence, and poor compliance.

Groups

Participants were dichotomized into “Low-Bother” and “High-Bother” groups based on responses to the urinary urgency bother question (5b) on the ICIQ-OAB survey (“How much does this bother you”). The question is ranked from 0-10, 0 being “not at all” and 10 being “a great deal”. Participants in the Low-Bother group scored 0-5, and participants in High-Bother group scored 6-10. In addition, to ensure an adequate separation, individuals who scored “2” on the urgency symptom question (ICIQ-question 5A) were excluded as this value denotes a middle-of-the-road urgency response.

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Table 1. Participant characteristics by urgency group

	Overall	Low-Bother	High-Bother	P*
Total (n)	36	15	21	--
Age	60.0 ± 10.0	55.8 ± 3.8	62.5 ± 3.2	0.24
BMI	32.6 ± 5.4	29.6 ± 7.6	34.5 ± 1.6	0.04*
Race (n, %W)	31 (86.1)	14 (93.3)	17 (81.0)	0.38

BMI = Body Mass Index (Kg/M²), W = White. Data reported as mean ± SD and compared with t-tests. *P<0.05.

Table 2. ICIQ-OAB and OAB-V3 survey scores by urgency group

Surveys	Total		Low		High		p-value	
	36		15		21		--	
ICIQ-OAB	S	B	S	B	S	B	p ^S	p ^B
ICIQ-Frequency	1.19	5.69	1.13	4.07	1.23	6.86	0.79	0.01*
ICIQ-Nocturia	2.11	5.31	1.73	3.13	2.38	6.86	0.10	<0.01*
ICIQ-Urgency	2.25	6.03	1.40	2.60	2.86	8.48	<0.01	<0.01*
ICIQ-UI	2.22	6.92	1.33	3.80	2.86	9.14	<0.01	<0.01*
OAB-V3	B		B		B		P	
OAB-V3-Frequency	3.17		2.80		3.45		0.26	
OAB-V3-Urgency	3.46		2.26		4.35		<0.01*	
OAB-V3-UI	3.51		2.47		4.30		<0.01*	

S = Score (0-4), B = Bother (0-10), UI = Urge Incontinence, Low = Low-Bother, High = High-Bother. Data reported as means and compared with t-tests. *P<0.05.

Statistical analysis

Parametric data are reported as means ± standard error (SE) unless otherwise stated. For categorical variables, one-tailed chi-square tests were used as a one-way response was noted. For continuous variables, two-tailed Students t-tests were used. Statistical software included Excel (Microsoft: Redmond, WA) and GraphPad (Dotmatics: Boston, MA). Statistical significance was determined as P<0.05.

Results

Forty-seven participants were recruited. Five males were excluded (due to small sample size). In addition, four females who scored ≥3 on all three neutral questions of the short form cues survey (indicating acquiescence bias), and two females who scored “2” on ICIQ-OAB urgency question (Q5a) were excluded. Therefore, the total group (N = 36) was 100% biological females with a mean age of 60.0 ± 10 years. Based on survey responses, there were 15 participants (41.6%) in the Low-Bother group and 21 (58.3%) in the High-Bother group. The groups did not differ based on age or racial

makeup. However, average BMI was higher in the High-Bother group (P<0.05) (**Table 1**).

OAB survey data, as expected, showed differences in symptoms and bother between urgency groups (**Table 2**). Overall, 30/35 patients (85.7%) met criteria for OAB based on the OAB-V3 instrument (note: one participant did not complete the survey). All ICIQ-OAB bother scores were higher in the High-Bother compared to the Low-Bother group, justifying OAB bother as an appropriate measure to dichotomize groups. However, in terms of symptom severity, only urgency and urge incontinence scored significantly higher in this

group. Likewise, in the OAB-V3, bother associated with urgency and urge incontinence, but not urinary frequency, was higher in the High-Bother group.

Urodynamic testing diagnostic results showed no differences in any of the listed parameters except for urodynamic stress urinary incontinence, identified in 40% of the low and 85% of the high bother group (P<0.05) (**Table 3**).

Long-form cue survey responses are shown in **Table 4** which compares environmental, mood, cognitive, and unlikely urgency cues between Low and High-Bother groups. The High-Bother group demonstrated significantly greater cue responses on 11 of 37 items (29.7%), but none of these were detected in the Low-Bother group (P<0.05). Environmental cues associated with physical activity (i.e., rising to a standing position) were not analyzed as these are more likely to represent abnormal anatomy such as sphincteric dysfunction. Positive cue responses in the High-Bother group included three mood cues (worried, tired, depressed), five environmental cues (running water, arrival at home, cold exposure, near bathroom often or occasionally

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Table 3. Urodynamic findings by urgency group

UD Finding (n, %)	Total	Low-Bother	High-Bother	p-value*
Totals	35	15	20	--
Detrusor Overactivity	4 (11.4)	1 (7.0)	3 (15.0)	0.44
Neurogenic Voiding Dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	1
Elevated Post Void Residual	1 (3.0)	1 (7.0)	0 (0.0)	0.24
Detrusor Underactivity	3 (9.0)	0 (0.0)	3 (15.0)	0.12
Decreased Sensation	7 (20.0)	3 (20.0)	4 (20.0)	1
Voiding Dysfunction	5 (14.0)	3 (20.0)	2 (10.0)	0.4
Stress Urinary Incontinence	23 (66.0)	6 (40.0)	17 (85.0)	0.01*
Poor Compliance	2 (6.0)	1 (7.0)	1 (5.0)	0.83

UD = urodynamics. *P<0.05.

Table 4. Percentage of positive long form cue responses by urgency group

Positive Long Form Cues (n, %)	Low-Bother	High-Bother	P
Total Participants	15	21	--
When you don't know bathroom location ^C	5 (33.3)	14 (66.7)	0.02*
Running water ^E	7 (46.7)	17 (81.0)	0.02*
Arrival at home ^E	9 (60.0)	18 (85.7)	0.04*
Cold weather or cold places ^E	2 (13.4)	9 (42.9)	0.03*
When near bathroom often used ^E	6 (40.0)	16 (76.2)	0.01*
When near bathroom occasionally used ^E	5 (33.3)	13 (61.9)	<0.05*
Being worried ^M	3 (20.0)	11 (52.3)	0.02*
When you are tired ^M	3 (20.0)	11 (52.4)	0.02*
When you are especially depressed ^M	1 (6.7)	7 (33.3)	0.03*
Call on phone when at home ^U	0 (0.0)	6 (28.6)	0.01*
Call on phone when away from home ^U	0 (0.0)	5 (23.8)	0.02*

C = Cognitive, E = Environmental, M = Mood, U = Unlikely. *P<0.05. Positive response defined as score ≥3 on long form cues survey (scale: 1-5). Note: Only 11 of 36 total cues with significant difference between groups are shown.

used) and one cognitive cue (don't know the location of a bathroom). However, two unlikely cues (getting a call at home and getting a call away from home) were also positive, suggesting some acquiescence bias.

Responses to the short form cues survey are shown in **Table 5** where only running water was positive in the High-Bother group (P<0.05). Comparison of positive cue responses between the long and short form surveys identified only "running water" as a positive urgency cue in both surveys. There was good reproducibility between studies with 86% of participants having similar positive cues on both surveys.

Discussion

The key finding of this study was that individuals with High-Bother urinary urgency are more

likely to report positive cue responses which can lead to increased urinary urgency. Although multiple environmental, mood, and cognitive cues were associated with high-bother urinary urgency, only exposure to "running water" was significantly associated with High-Bother urgency in both the long and short form surveys. This suggests the potential existence of a cue-responsive OAB phenotype which may be identified by survey questions or even experimentally identified through exposure to running water.

In this study, participants were grouped as a function of urgency bother (High-Bother vs. Low-Bother groups) rather than symptom severity. This was important because bother symptoms were significantly different in all OAB categories (frequency, nocturia, urgency, and urge incontinence), but severity scores

were more variable. In addition, OAB bother is likely a stronger driver of quality of life impact [3, 17].

Prior studies regarding cue responsivity show similar findings as our current investigation, and, it is estimated that approximately 60% of individuals with OAB will experience some form of urgency cue [13, 18]. Ghei et al [19], administered a computer-based survey to patients attending a clinic for OAB. Patients were asked to grade experiences of both urgency and potential cues which provoke urgency. The authors found an association with cues, including running water and cold exposure, and OAB symptom severity. O'Connell and colleagues administered a urinary cues survey to women with and without OAB and found that OAB patients had significantly higher situational "cues" scores [13, 18] which is consistent with

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Table 5. Percentage of positive short form cue responses by urgency group

Cues (N, %)	Low-Bother	High-Bother	P
Totals	15	21	–
Running Water	0 (0.0)	7 (33.3)	0.01*
Warm Weather ^N	0 (0.0)	1 (4.8)	0.58
Stressed/Anxious	1 (6.7)	4 (19.0)	0.29
Surfing Internet ^N	0	1 (4.8)	0.58
Cold Weather	0	3 (14.3)	0.25
Relaxed/Calm ^N	0	1 (4.8)	0.58

Positive cue response defined as score ≥ 3 on short form cues survey (scale: 0-4). * $P < 0.05$. N = neutral questions.

our current results. However, the main advance in the current study is the well-characterized nature of participants with two validated OAB survey instruments [8, 11], the validated urinary cues questionnaire [13, 18], and a new short-form cues survey (**Appendix 1**). In addition, urodynamic results were included in this study and demonstrated minimal differences in groups other than higher rates of stress urinary incontinence.

Running water, the only cue in this study associated with high urgency in both the validated long-form cues survey [13, 18] and our new short-form survey, has a well-known, but poorly quantified association with urgency and urge incontinence [15, 19]. The sound of running water causing increased urinary urgency has been studied since the 1970s [20]. Multiple hypotheses explaining this phenomenon have been explored including Pavlovian conditioning, increased parasympathetic tone, and increased physical and emotional relaxation [21, 22]. Specifically, parasympathetic tone from hearing the sound of running water may cause decreased urethral sphincter tone and subsequently an increased peak flow rate [21].

Acquiescence bias is described as a patient's tendency to agree with survey statements regardless of its content [23]. In studies of OAB, because OAB symptoms negatively affect quality of life, participants are more likely to rank any cue questions (even expected neutral cues) as triggers of urgency [24]. Participant attitudes may also influence self-reported symptoms [25]. In our study, several unlikely cues were found to be significantly associated with high urgency bother, suggesting the presence of acquiescence bias seen in patients who are

particularly bothered by their symptoms. To account for this, we excluded participants who had a positive cue response on all three neutral questions in our six-item short-form cues survey. However, even with this control, the finding of two elevated neutral cue responses suggests the need for further research to identify specific cue-responsive OAB phenotypes.

Mood has long been associated with OAB. Increased symptoms of anxiety and depression have a greater impact on patients with OAB than those without OAB [26, 27]. In both the novel Short Form Cues survey and Long Form Cues survey, a variety of mood symptoms were associated with elevated urgency including being worried, stressed, or anxious. Multiple studies show an association with mood and voiding dysfunction [28]. Anxiety and urinary symptoms including frequency and urgency have been shown to interact and influence one another; patients with OAB and anxiety have reported increased severity of symptoms and worse quality of life [29, 30]. Altered mood, associated with dysfunctional neurotransmitter processes in patients with depression, has been hypothesized to impact bladder neural signaling potentially leading to urinary incontinence or increased urgency [29, 30]. Additionally, the impact of OAB symptoms on quality of life may lead to increased isolation and depressed mood [31].

Limitations of the current investigation include the presence of acquiescence bias and a relatively small sample size. However, this is the only known cues study which provides comprehensive participant evaluation including three validated surveys, a novel short-form cues survey, and a complete urodynamics evaluation. A larger sample size may identify more significant cue associations as some relationships neared significance.

Conclusions

This study demonstrated that patients with high-bother urinary urgency may have symptom responses to environmental, mood, and cognitive cues. Specifically, exposure to the sound of running water, may trigger urgency symptoms. This suggests increased sensitivity to cues amongst participants with bothersome OAB and the potential presence of a cue-specific

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OAB phenotype. However, further research is required to identify and experimentally test how specific cues can trigger urgency.

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Disclosure of conflict of interest

None.

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Initial Number

ICIQ-OAB (US English) 11/05
CONFIDENTIAL

MONTH DAY YEAR
Today's date

Overactive bladder

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much these symptoms bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

MONTH DAY YEAR

2. Are you (check one):

Female Male

3a. How many times do you urinate during the day?

1 to 6 times 0
7 to 8 times 1
9 to 10 times 2
11 to 12 times 3
13 or more times 4

3b. How much does this bother you?

Please circle a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

4a. During the night, how many times do you have to get up to urinate, on average?

none 0
one 1
two 2
three 3
four or more 4

4b. How much does this bother you?

Please circle a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

5a. Do you have to rush to the toilet to urinate?

never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

5b. How much does this bother you?

Please circle a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

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ICIQ-OAB (US English) 11/05

6a. Does urine leak before you can get to the toilet?

- | | | |
|------------------|--------------------------|---|
| never | <input type="checkbox"/> | 0 |
| occasionally | <input type="checkbox"/> | 1 |
| sometimes | <input type="checkbox"/> | 2 |
| most of the time | <input type="checkbox"/> | 3 |
| all of the time | <input type="checkbox"/> | 4 |

6b. How much does this bother you?

Please circle a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

© ICSmale/BFLUTS

Thank you very much for answering these questions.

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VCU CUES SURVEY:

Participant #: _____

Date: _____

Below is a list of possible “triggers” that might make people have to rush to the toilet to urinate. Please answer based on your average experience in the last month.

Q1. Does the sound or sight of running water make you feel like you have to rush to the toilet to urinate?

- 0) Never
- 1) Occasionally
- 2) Sometimes
- 3) Most of the time
- 4) All of the time

Q2. Does warm weather make your feel like you have to rush to the toilet to urinate?

- 0) Never
- 1) Occasionally
- 2) Sometimes
- 3) Most of the time
- 4) All of the time

Q3. Does being stressed or anxious make you feel like you have to rush to the toilet to urinate?

- 0) Never
- 1) Occasionally
- 2) Sometimes
- 3) Most of the time
- 4) All of the time

Q4. Does surfing on the internet make you feel like you have to rush to the toilet to urinate?

- 0) Never
- 1) Occasionally
- 2) Sometimes
- 3) Most of the time
- 4) All of the time

Q5. Does cold weather make you feel like you have to rush to the toilet to urinate?

- 0) Never
- 1) Occasionally
- 2) Sometimes
- 3) Most of the time
- 4) All of the time

Q6. Does being relaxed or calm make you feel like you have to rush to the toilet to urinate?

- 0) Never
- 1) Occasionally
- 2) Sometimes
- 3) Most of the time
- 4) All of the time