A Randomized Controlled Trial of Device Guided, Slow-Paced Respiration in Women with Overactive Bladder Syndrome

Alison J. Huang,* Deborah Grady, Wendy B. Mendes, Cesar Hernandez, Michael Schembri† and Leslee L. Subak

From the Departments of Medicine (AJH, DG, CH), Urology (AJH), Psychiatry (WBM) and Obstetrics, Gynecology and Reproductive Sciences (MS), University of California-San Francisco, San Francisco and Department of Obstetrics and Gynecology, Stanford University (LLS), Stanford, California

Purpose: We evaluated the effects of device guided, slow-paced respiration on urgency associated urinary symptoms, perceived stress and anxiety, and autonomic function in women with overactive bladder syndrome.

Materials and Methods: We performed a randomized, parallel group trial of slow-paced respiration to improve perceived stress and autonomic dysfunction as potential contributors to overactive bladder. Ambulatory women who reported at least 3 voiding or incontinence episodes per day associated with moderate to severe urgency were randomized to use a portable biofeedback device to practice daily, slow, guided breathing exercises or a control device which appeared identical and was reprogrammed to play music without guiding breathing. During 12 weeks we evaluated changes in urinary symptoms by voiding diaries, perceived stress and anxiety by validated questionnaires, and autonomic function by heart rate variability and impedance cardiography.

Results: In the 161 randomized participants, including 79 randomized to paced respiration and 82 randomized to the control group, the average ± SD baseline frequency of voiding or incontinence associated with moderate to severe urgency was 6.9 ± 3.4 episodes per day. Compared to controls the participants randomized to paced respiration demonstrated greater improvement in perceived stress (average Perceived Stress Scale score decrease 2.8 vs 1.1, p=0.03) but not in autonomic function markers. During 12 weeks the average frequency of voiding or incontinence associated with moderate to severe urgency, which was the study primary outcome, decreased by a mean of 0.9 ± 3.2 episodes per day but no significant between group difference was detected.

Conclusions: Among women with overactive bladder slow-paced respiration was associated with a modest improvement in perceived stress during 12 weeks. However, it was not superior to a music listening control for reducing urinary symptoms or changing autonomic function.

Key Words: urinary bladder, overactive; breathing exercises; relaxation therapy; stress, psychological; autonomic nervous system

Abbreviations and Acronyms

HADS = Hospital Anxiety and Depression Scale
OAB = overactive bladder
OAB-Q = OAB Questionnaire
PEP = pre-ejection period
PPBC = Patient Perception of Bladder Condition
PSS = Perceived Stress Scale
RSA = respiratory sinus arrhythmia
STAI = State Trait Anxiety Inventory
USIQ = Urgency Severity and Impact Questionnaire

OVERACTIVE bladder, a syndrome characterized by strong recurrent urges to urinate (ie urgency), increased frequency of daytime and nighttime urination, and in some patients urgency incontinence, affects up to 1 of 5 women and can have a major impact on functioning and quality of life.[1,2] Currently the most widely used treatment of OAB is antimuscarinic

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* Correspondence: Department of Urology, University of California-San Francisco, 1545 Divisadero St., San Francisco, California 94115 (telephone: 415-514-8697; FAX: 415-514-8686; e-mail: Alison.Huang@ucsf.edu).

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medications, which are modestly effective in decreasing urgency associated voiding but associated with side effects[3] and a high discontinuation rate.[4] While behavioral management techniques such as bladder retraining are better tolerated, many patients have difficulty practicing them effectively without intensive training from specialized practitioners.[5] As a result, alternate treatment strategies are needed which are safer and more accessible.

Epidemiological studies have documented strong associations of perceived stress and anxiety with urinary urgency in women with OAB, including an increased risk of new onset OAB among those with high baseline levels of stress or anxiety.[6,7] Clinical studies have also indicated that patients with OAB tend to have abnormalities in peripheral autonomic function, which are in turn associated with clinical anxiety disorders.[8–10] These findings have generated interest in identifying alternate therapeutic approaches directed at improving perceived stress, anxiety and associated autonomic dysfunction as potential contributors to OAB.[11,12]

One such potential therapy is slow-paced respiration, a behavioral technique involving slowing the respiratory rate to below 10 breaths per minute with the goal of improving perceived stress, anxiety and autonomic balance. Slow breathing exercises are already used to a limited extent in urge suppression techniques for OAB, in that patients are told to take slow, deep breaths upon experiencing an urge to urinate to distract themselves from the bladder sensation. However, to our knowledge prior research has not determined whether slow breathing may be useful, not just as an ad hoc response to isolated episodes of urgency but also as a regular program of breathing exercises to alter underlying susceptibility to OAB.

MATERIALS AND METHODS

The CURE (Controlling Urgency through Relaxation Exercises) study is a randomized, parallel group trial of device guided, slow-paced respiration in women with OAB. Participants were ambulatory women recruited from 2014 to 2017 at 2 study clinics in San Francisco and Oakland, California affiliated with UCSF (University of California-San Francisco). Women were eligible for study if they documented an average of at least 3 voiding or incontinence episodes per day associated with at least a moderate sensation of urgency in a voiding diary[13] and they agreed to temporarily forego other clinical OAB treatments.

Women were excluded if they reported a history of pelvic cancer or irradiation, prior bladder surgery or other pelvic surgery in the last 3 months, interstitial cystitis, bladder or rectal fistula, a congenital urinary tract defect, symptomatic pelvic organ prolapse, 3 or more recurrent urinary tract infections per year or major neurological conditions such as stroke or multiple sclerosis. Additionally, women could not have evidence of hematuria or infection on screening urinalysis, be pregnant or planning pregnancy, or have a chronic pulmonary condition which would interfere with slow breathing exercises. Women receiving anxiolytics or antidepressants were required to be on a steady dose for a month. No exclusions were made for the use of β or α blocker, or agonist medication. Although women engaged in practitioner administered behavioral relaxation therapies were excluded from study, participants were not precluded from using other informal self-administered relaxation practices.

All participants provided written informed consent. The study was approved by the UCSF Institutional Review Board (No. 14-13319) and registered on ClinicalTrials.gov (NCT02202031).

Participants were randomly assigned in equal ratios to the paced respiration or the control intervention by a computer algorithm using randomly permuted block sizes of 2, 4 and 6. Women assigned to paced respiration were instructed to use the commercially available RESPeRATE® portable biofeedback device, which is currently approved by the Food and Drug Administration for adjunctive treatment of hypertension based on evidence that regular use decreases high blood pressure attributable to excess sympathetic tone.[14–16] The device senses the respiratory rate of the user using an elastic belt placed around the chest and it plays musical tones synchronized to inspiration and expiration. The device gradually increases the interval between musical tones to guide the user in slowing respiration and expiration. Consistent with hypertension use, the CURE participants randomized to paced respiration were instructed to practice slowing respiration for a minimum of 15 minutes per day for 12 weeks.

To enable rigorous evaluation of efficacy participants randomized to the control group were given an identically appearing RESPeRATE device reprogrammed to play quiet nonrhythmic music while monitoring spontaneous breathing. They were also instructed to use it for a minimum of 15 minutes per day for 12 weeks. Participants and study staff responsible for monitoring adherence were aware of the intervention assignment.

Adherence to device use was recorded automatically by the devices in each group. All participants also received basic written information about behavioral self-management strategies for OAB, including timed urination and urge suppression, consistent with usual first line care.

OAB symptoms were assessed at baseline and 12 weeks using a validated 3-day voiding diary administered in previous OAB trials.[13] Participants recorded each time that they experienced an urge to urinate, voided in the toilet or leaked urine and they rated the severity of urgency associated with each episode using a standardized scale of none, mild, moderate or severe.[17] Diary data were abstracted by research staff blinded to the intervention assignment. An OAB composite score was calculated which assigned points to voiding and incontinence based on associated urgency.[17]

Participants also completed structured item, validated questionnaires of the severity or the impact of urinary

symptoms at baseline and 12 weeks, including the OAB-Q,[18] the USIQ[19] and the PPBC.[20] Additional questionnaires were used to assess perceived stress and associated anxiety symptoms at baseline and at 12 weeks, including the Cohen PSS to assess subjective feelings and thoughts related to perceived stress,[21] the STAI trait component to assess somatic anxiety[22] and the anxiety subscale of the HADS to assess cognitive anxiety.[23] Table 1 shows score range and directionality.

Among participants enrolled in San Francisco resting cardiac autonomic function was assessed by electrocardiography derived heart rate variability and impedance cardiography at baseline and 12 weeks. Standardized procedures for these measurements were described previously.[24] Briefly, while sitting in a quiet, ambient temperature room, participants were outfitted with a standard tetrapolar electrode system composed of 2 inner electrodes placed at the xiphisternal joint and the base of the neck with outer electrodes place 3 cm distal to the inner electrodes. Participants were then asked to view a neutral video for at least 5 minutes while resting measurements were sampled at 1,000 Hz. Measurements were stored using an MP150 data acquisition system (Biopac®).

To assess sympathetic autonomic activity measurements focused on the PEP, that is the period from the start of cardiac ventricular depolarization to aortic valve opening. The PEP provides a measure of ventricle contractility, which has been shown to be a relatively pure measure of sympathetic activity since it occurs during systole, when there are no parasympathetic influences on the cardiac cycle. Increases in peripheral sympathetic nervous system activity correspond to a shortening PEP.[25]

To assess parasympathetic activity analyses focused on RSA. This is heart rate variability during the typical respiratory cycle, which is measured by heart rate variability in the high frequency range, reflecting the amount of influence of the cardiac vagus nerve with higher RSA corresponding to greater peripheral parasympathetic activity.[26] Although to our knowledge there are no validated thresholds to classify subjects with abnormal sympathetic or parasympathetic tone based on the PEP or RSA, prior studies have mentioned a mean ± SE PEP of 102 ± 4.1 and a mean RSA of 6.5 ± 3.9 in healthy community populations.[27,28]

Adverse events were assessed at 1, 6 and 12-week followups by asking participants whether they had experienced any negative change in health. Serious adverse events were defined as death, hospitalization or disability. The primary study outcome was the 12-week change in the frequency of voiding or incontinence episodes associated with at least moderate urgency. Secondary outcomes included the 12-week change in the frequency of voiding or incontinence associated with severe urgency, urgency type incontinence, daytime and nighttime voiding, the OAB symptom composite score, and the OAB-Q, USIQ and PPBC scores.

A sample size of 160 subjects (80 per group) was selected to provide 80% power on 2-sided tests with a 5% type I error to detect a between group difference of more than 20% in the primary outcome in the paced respiration group vs the control group. This assumed a mean 30% reduction in outcome frequency among controls, a 0.59 correlation between baseline and followup, and a 15% loss to followup.

Baseline characteristics of participants as well as adherence to interventions at followup visits were examined with descriptive statistics. Between group differences in baseline characteristics were assessed using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. ANCOVA models were developed to estimate least square mean changes in all outcomes in each intervention group during 12 weeks and test for between group differences while adjusting for baseline values. Change values were 98% to 99% winsorized if indicated by visual inspection of Q-Q plots. Models examining intervention effects on autonomic outcomes were further adjusted for diabetes mellitus, which was unequally distributed between the groups at baseline in the subset of women who provided autonomic data as well as information on β or α blocker, agonist or sympathomimetic medication.

Only participants who provided 12-week data were included in the initial intervention effects models. However, to examine the implications of missing data 15 multiple imputed data sets were created using the Markov chain Monte Carlo method[29] and summary effect estimates with the SE were calculated using standard methods for imputed data. All analyses were performed with SAS®, version 9.4.

RESULTS

A total of 833 women were contacted, of whom 631 completed screening and 161 were found eligible and randomized, including 79 to paced respiration and 82 to the control group (see figure). The most common single reason for study ineligibility was insufficient frequency of urgency associated urinary symptoms. Five women (10%) assigned to paced respiration and 6 (7%) who served as controls discontinued participation early.

At baseline participants reported an average of 6.9 ± 3.4 moderate to severe urgency associated voiding or incontinence episodes, 1.3 ± 1.0 nocturnal voiding episodes and 1.3 ± 2.0 urgency incontinence episodes per day (table 1). Mean PSS questionnaire scores were close to the threshold of 14 used to indicate increased perceived stress but mean scores on other anxiety measures were below standard thresholds of clinically significant anxiety. No significant between group differences were detected in outcome measures at baseline.

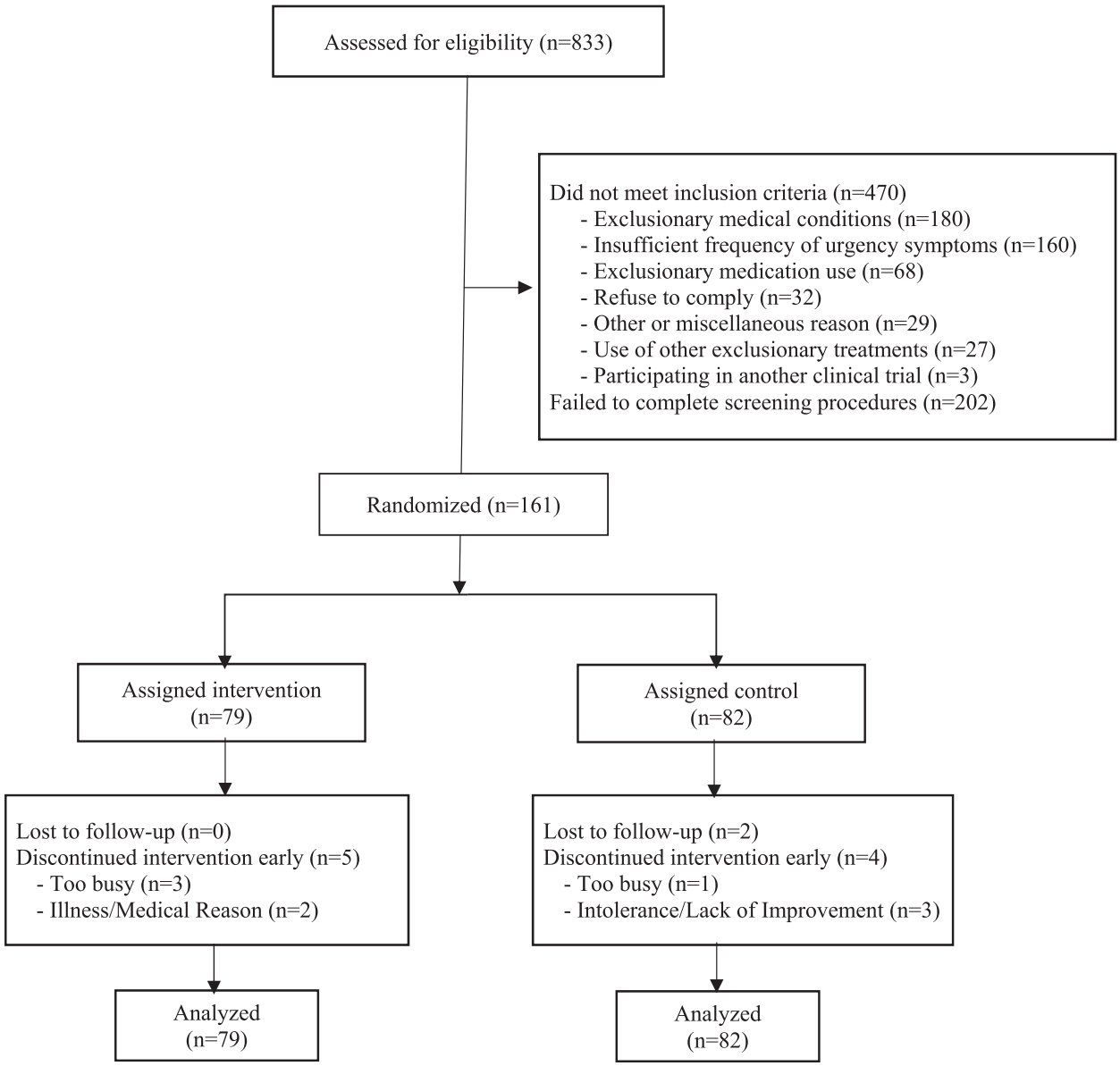
Of the 150 participants who completed the 12-week visit those in the paced respiration and control groups practiced the assigned intervention an average of 4.8 and 5.5 days per week, respectively, at 12 weeks (table 2). On those days they practiced an average of 16.8 and 16.4 minutes per day in the paced respiration and control groups, respectively.

Participants in each group reported modest decreases in the frequency of OAB symptoms,

Table 1. *Baseline participant demographic and clinical characteristics by intervention assignment*

	Paced Respiration		Music Control		p Value (chi-square or Kruskal-Wallis test)
No. pts	79		82		
Mean ± age	60.4 ± 11.4		61.7 ± 10.9		0.42
No. race/ethnicity (%):					0.53
NonLatina Caucasian	40	(50.6)	49	(59.8)	
Latina Caucasian	12	(15.2)	6	(7.3)	
Asian/Asian American	8	(10.1)	6	(7.3)	
African American	12	(15.2)	12	(14.6)	
Mixed race	5	(6.3)	8	(9.8)	
Unknown	2	(2.5)	1	(1.2)	
No. self-reported general health (%):					0.29
Excellent	19	(24.1)	28	(34.1)	
Very good	36	(45.6)	31	(37.8)	
Good	22	(27.8)	18	(22.0)	
Fair/poor	2	(2.5)	5	(6.1)	
No. selected medication (%):					
Diuretic (thiazide or other nonloop)	8	(16.7)	5	(8.3)	0.19
Sedative/hypnotics	1	(2.1)	2	(3.3)	0.69
Tricyclic antidepressants	4	(8.3)	3	(5.0)	0.48
Selective serotonin/norepinephrine reuptake inhibitors	9	(18.8)	11	(18.3)	0.96
Other antidepressants	2	(4.2)	1	(1.7)	0.43
β blockers	5	(6.3)	13	(15.9)	0.06
β agonists	0	(0.0)	1	(1.2)	0.33
α blockers	2	(2.5)	1	(1.2)	0.54
Sympathomimetics	2	(2.5)	1	(1.2)	0.54
No. parity (%):					0.30
0	19	(24.1)	19	(23.2)	
1 or 2	35	(44.3)	28	(34.1)	
3 or More	25	(31.6)	35	(42.7)	
No. gynecologic history (%):					
Postmenopausal	62	(78.5)	68	(82.9)	0.47
Oophorectomy	13	(16.5)	15	(18.3)	0.76
Hysterectomy	14	(17.7)	11	(13.4)	0.45
No. health related habits (%):					
Current cigarette smoking	0	(0.0)	3	(3.7)	0.08
Weekly alcohol consumption	34	(43.0)	44	(53.7)	0.18
Mean ± SD physical examination measures:					
Body mass index (kg/m^2)	27.8 ± 5.8		28.4 ± 7.7		0.97
Blood pressure (mm Hg):					
Systolic	122.1 ± 17.4		119.8 ± 15.3		0.42
Diastolic	75.4 ± 10.3		74.4 ± 9.1		0.49
Median No. incontinence or voiding episodes/day (IQR):	6.7	(4.7, 9.3)	6.0	(4.0, 8.0)	0.16
At least severe urgency	2.3	(1.3, 4.0)	2.0	(0.7, 3.0)	0.09
Urgency	0.7	(0.0, 2.0)	0.7	(0.0, 1.7)	0.89
Daytime voiding regardless of urgency	9.3	(8.0, 11.7)	8.7	(7.3, 11.0)	0.29
Nighttime voiding regardless of urgency	1.0	(0.3, 2.0)	1.3	(0.7, 2.0)	0.23
OAB composite score*	28.0	(21.3, 34.7)	24.3	(20.0, 31.0)	0.16
Urinary symptom questionnaire scores:					
Median OAB-Q (IQR)†	29.7	(21.2, 41.2)	30.0	(20.6, 38.8)	0.83
Mean ± SD USIQ Severity Subscale‡	58.5 ± 14.5		58.5 ± 11.7		0.79
Mean ± SD USIQ Quality of Life Subscale‡	24.6 ±19.4		21.9 ± 15.4		0.69
Median Urogenital Distress Inventory-Short Form (IQR)§	44.4	(33.3, 61.1)	44.4	(33.3, 55.6)	0.84
Median PPBC (IQR)¶	3.0	(2.0, 3.0)	3.0	(2.0, 3.0)	0.87
Median stress + anxiety questionnaire scores (IQR):					
PSS‖	14.0	(8.0, 20.0)	13.0	(9.0, 18.0)	0.41
STAI-Trait Component**	37.0	(31.0, 45.0)	35.5	(28.0. 44.0)	0.33
HADS-Anxiety Subscale††	7.0	(4.0, 10.0)	6.0	(3.0, 9.0)	0.37
Mean ± SD msec autonomic function parameters (range):‡‡					
Pre-ejection period (msec)	117.1 ± 14.8	(78.0, 144.6)	123.1 ± 11.5	(102.4, 149.6)	0.16
Respiratory sinus arrhythmia (msec^2)	5.7 ± 1.6	(2.3, 9.4)	4.8 ± 1.2	(1.7, 6.4)	0.052

* Calculated by assigning points for mild (1), moderate (2) and severe (3) urgency associated voiding and urgency incontinence (5 points each), and averaging across days.
† Scored from 0 to 100 with higher scores indicating greater OAB bother and impact.
‡ Scored from from 0 to 100, with higher scores indicating greater severity and impact of urinary symptoms.
§ Scored from 0 to 75 with higher scores indicating greater urogenital symptom bother.
¶Scored using a 6-point Likert scale, with higher scores indicating greater perception of bladder-related problems.
‖ Scored from 0 to 40, with higher scores indicating greater perceived stress.
** Trait component scored from 20 to 80, with higher scores indicating greater somatic anxiety.
†† Scored from 0 to 21 with higher scores indicating greater cognitive anxiety.
‡‡ Collected at baseline among the 30 women in the paced respiration and 22 women in the music control group at the San Francisco site.



CONSORT (Consolidated Standards of Reporting Trials) diagram of participant recruitment, randomization and followup

Table 2. *Adherence to intervention practice by intervention assignment and time point*

Practice	Paced Respiration	Music Listening	p Value
Mean ± SD No. days/wk:			
Wk 1	5.6 ± 1.6	5.7 ± 1.4	0.71
Wk 6	5.1 ± 1.6	5.5 ± 1.3	0.18
Wk 12	4.8 ± 2.1	5.5 ± 2.1	0.048
Mean ± SD on practice days (mins/day):			
Wk 1	15.2 ± 2.7	15.5 ± 2.7	0.78
Wk 6	16.7 ± 3.4	16.2 ± 3.1	0.10
Wk 12	16.8 ± 4.0	16.4 ± 5.3	0.17

*Practice adherence assessed by reviewing downloaded RESPeRATE data among participants confirmed to have received assigned intervention, including 77 women in paced respiration group at week 1, 74 at week 6 and 74 at week 12, and in the music listening group 79 at week 1, 78 at week 6 and 76 at week 12.

including voiding or incontinence episodes associated with at least moderate urgency, during the 12 weeks (table 3). However, no significant between group differences were detected in a change in OAB symptoms. Participants in each group also demonstrated modest improvements in multiple urinary symptom questionnaire scores during the 12 weeks but the changes did not differ significantly between the groups (table 3). Findings were not significantly affected by analyses using multiple imputation to account for missing data.

Average scores on perceived stress and anxiety symptom questionnaires decreased modestly in the 2 groups during 12 weeks (table 4). Participants

Table 3. *Average change in urinary symptom frequency and urinary symptom questionnaire scores in 12 weeks by intervention assignment*

	Paced Respiration		Music Control		Between Group Difference	
	Mean (95% CI)*	p Value	Mean (95% CI)*	p Value	Mean (95% CI)*	p Value
Diary urinary symptom frequency:						
Incontinence or voiding episodes associated with at least moderate urgency/day	−0.8 (−1.5, −0.1)	0.02	−1.1 (−1.7, −0.4)	<.01	0.2 (−0.7, 1.2)	0.62
Incontinence or voiding episodes associated with severe urgency/day	−0.9 (−1.3, −0.6)	<0.01	−0.9 (−1.2, −0.5)	<0.01	−0.1 (−0.6, 0.5)	0.77
Urgency incontinence episodes/day	−0.6 (−0.8, −0.3)	<0.01	−0.6 (−0.9, −0.4)	<0.01	0.1 (−0.2, 0.4)	0.65
Daytime voiding episodes/day regardless of urgency	−0.7 (−1.1, −0.3)	<0.01	−0.8 (−1.2, −0.3)	<0.01	0.1 (−0.6, 0.7)	0.82
Nighttime voiding episodes/night regardless of urgency	−0.4 (−0.6, −0.2)	<0.01	−0.3 (−0.4, −0.1)	<0.01	−0.1 (−0.4, 0.1)	0.28
Total No. voiding episodes/day regardless of urgency	−1.1 (−1.5, −0.6)	<0.01	−1.0 (−1.5, −0.6)	<0.01	0.0 (−0.7, 0.6)	0.92
Modified OAB symptom composite score†	−3.2 (−4.9, −1.4)	<0.01	−3.6 (−5.4, −1.8)	<0.01	0.4 (−2.1, 2.9)	0.75
Urinary symptom questionnaire scores:						
Overall OAB-Q	−14.3 (−16.9, −11.7)	<0.01	−15.5 (−18.0, −12.9)	<0.01	1.2 (−2.5, 4.8)	0.54
OAB-Q bother subscale	−19.2 (−22.5, −15.8)	<0.01	−17.9 (−21.2, −14.6)	<0.01	−1.3 (−6.0, 3.4)	0.60
OAB-Q health related quality of life subscale	−12.8 (−15.4, −10.2)	<0.01	−14.6 (−17.1, −12.1)	<0.01	1.8 (−1.8, 5.4)	0.33
Severity USIQ subscale	−13.9 (−17.1, −10.6)	<0.01	−15.6 (−18.8, −12.3)	<0.01	1.7 (−2.9, 6.3)	0.47
Health related quality of life USIQ subscale	−10.2 (−13.2, −7.2)	<0.0001	−12.4 (−15.3, −9.4)	<0.0001	2.2 (−2.1, 6.4)	0.31
Urogenital Distress Inventory-Short Form	−17.1 (−20.9, −13.4)	<0.0001	−15.4 (−19.1, −11.6)	<0.0001	−1.8 (−7.1, 3.5)	0.51
PPBC	−0.9 (−1.1, −0.7)	<0.0001	−0.7 (−1.0, −0.5)	<0.0001	−0.1 (−0.4, 0.2)	0.36

* Least square mean estimates of change and 95% CI derived from ANCOVA models adjusted for baseline values.
† Calculated by assigning points per episode mild urgency associated voiding (1), moderate urgency associated voiding (2), severe urgency associated voiding (3) and urgency incontinence (5 points each) per day and averaging across all diary days with 0 point for voiding episodes without urgency.

assigned to slow-paced respiration demonstrated greater improvements in PSS scores than those assigned to music control but no other significant between group differences were observed in the change in anxiety or symptoms (table 4).

No significant within group changes in resting parasympathetic or sympathetic function were observed during 12 weeks in the 44 women who underwent autonomic function assessments at baseline and 12 weeks, including 25 in the paced respiration group and 19 in the control group (table 4). Additionally, no significant between group differences were noted in autonomic function.

On safety assessments 30 women assigned to paced respiration and 29 assigned to the control group reported 1 or more adverse events ($p=0.73$). There were no reports of serious adverse events or of any adverse events directly attributable to study interventions.

DISCUSSION

In this randomized trial women with OAB assigned to practice daily slow, guided breathing exercises reported greater improvement in perceived stress during 12 weeks relative to that in the control group which listened to music control. However, the improved group did not show greater improvement in the frequency of urgency associated voiding or incontinence, in other OAB questionnaires or in autonomic function. Although paced respiration has been used successfully to treat other conditions associated with high perceived stress and/or peripheral autonomic dysfunction, our findings do not support paced respiration as a uniquely effective treatment of OAB.

Slow breathing has already been incorporated to a limited extent into conservative urge suppression distraction and relaxation techniques to manage acute urgency episodes in OAB cases. When feeling

Table 4. *Change in perceived stress, anxiety and depression measures, and sympathetic and parasympathetic autonomic function markers in 12 weeks by intervention assignment*

	Paced Respiration		Music Control		Between Group Difference	
	Mean (95% CI)*	p Value	Mean (95% CI)*	p Value	Mean (95% CI)*	p Value
Measures:		<0.01				
PSS	−2.8 (−4.0, −1.7)		−1.1 (−2.2, −0.0)	0.05	−1.7 (−3.3, −0.1)	0.03
STAI-Trait Component	−2.9 (−4.3, −1.4)		−2.4 (−3.8, −1.0)	<0.01	−0.4 (−2.4, 1.6)	0.67
HADS-Anxiety Subscale†	−1.4 (−1.9, −0.9)		−0.7 (−1.2, −0.2)	<0.01	−0.7 (−1.4, 0.1)	0.08
Markers:†						
Pre-ejection period (msec)	0.34 (−20.2, 20.9)	0.97	−3.4 (−21.9, 15.1)	0.72	3.8 (−7.1, 14.6)	0.49
Respiratory sinus arrhythmia ($msec^2$)	−0.27 (−1.1, 0.6)	0.52	−0.4 (−1.1, 0.3)	0.27	0.14 (−0.3, 0.6)	0.56

* Least square mean estimates of change and 95% CIs derived from ANCOVA models and adjusted for baseline values.
† Estimated mean changes represent raw values and due to skewed distribution p values were derived from models using winsorized (98-99th percentile) values.

the urge to urinate, patients are often told to sit or stand still, take deep, slow breaths and try to distract themselves from the bladder sensation. When combined with other behavioral modification strategies, urge suppression appears moderately effective in reducing OAB symptoms.[30] However, to our knowledge the breathing component of urge suppression has not previously been studied apart from other components of OAB self-management.

Slow-paced respiration has also been used to manage other chronic conditions associated with high levels of perceived stress or autonomic dysfunction. In particular the RESPeRATE guided breathing device is currently used for adjunctive treatment of hypertension.[14–16] However, in our study we did not detect significant changes in resting autonomic function associated with paced respiration in women with OAB. A recent trial of the RESPeRATE for a different indication (menopause related vasomotor symptoms) also indicated no significant effect on similar autonomic measures in women.[24]

This research benefits from the rigorous time equivalent control, the high retention rate and objective confirmation of intervention adherence. Nevertheless, several limitations should be noted. 1) Women were classified with OAB based on self-reported history and urinalysis testing without urodynamic or other clinical evaluation to further characterize pathophysiology. 2) The change in urinary symptoms was assessed by a voiding diary, which can be associated with measurement error despite its widespread use as an outcome measure in OAB trials. 3) While the music listening intervention was selected to rigorously control the time and attention spent on paced respiration, it was also an intervention with potential relaxing effects in its own right, which could have a role in improving participant perceived OAB symptoms. Consequently study results should not be used to draw conclusions about the effects of paced respiration vs no intervention at all. 4) Autonomic measurements were available only in the subset of participants seen at the San Francisco clinic, which may have limited our ability to detect changes in these outcomes. 5) Additionally, participants with OAB were not required to demonstrate clinically significant perceived stress or anxiety, or abnormal autonomic function at baseline, which may have resulted in ceiling/floor effects for these outcomes.

CONCLUSIONS

The findings of this randomized trial indicate that women with OAB who practice daily device guided, paced respiration exercises may experience greater improvement in perceived stress. However, they are no more likely to report improvement in urgency associated urinary symptoms than those who spend equivalent time listening to music. While behavioral relaxation based therapies may offer general benefits for OAB, this study does not support unique benefits of paced respiration for urgency associated urinary symptoms.

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