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What *Predicts* and What *Mediates* the Response of Urge Urinary Incontinence to Biofeedback?

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Abstract

Aims—To better target a behavioral approach for urge urinary incontinence (UUI) and enhance its efficacy by (1) identifying predictors of response to biofeedback-assisted pelvic muscle training (BFB), and (2) determining factors that mediate response.

Methods—BFB (4 biweekly visits) was administered to 183 women > 60 years (mean=73.6). Before and after intervention, all underwent comprehensive evaluation and videourodynamic testing. Postulated predictors and mediators from 4 urodynamic domains, specified *a priori*, were correlated with reduction in UUI frequency.

Results—Median UUI frequency decreased from 3.2/day to 1/day ($p=.0001$). UUI improved by 50% in 55% of subjects and by 100% in 13% of subjects. Frequent UUI predicted poor response ($p < 0.01$). Of the urodynamic parameters, only high amplitude and briskness of detrusor overactivity (DO) predicted decreased response ($p < 0.05$ and $p < 0.01$) and these could be measured only in the 43% of subjects with elicitable DO. Decreased DO elicibility was the only urodynamic variable that changed in concert with improvement and thus was a candidate mediator. Response was neither predicted nor mediated by proprioception/warning, cystometric capacity, detrusor contractility, sphincter strength, or baseline DO elicibility.

Conclusions—Severe DO predicts poor response to BFB. Good response is mediated by reduction in DO elicibility. Other than baseline UUI frequency, there are no other clinically or urodynamically important predictors or mediators of BFB response in this population. BFB may be best for patients with less severe DO. Future research to enhance its efficacy might better focus on the brain than on the lower urinary tract.

Keywords

behavioral therapy; detrusor overactivity; overactive bladder; aged; women; urodynamics; mechanisms

1. Introduction

Urge urinary incontinence (UI) is prevalent, morbid and costly, especially among older women.¹ Unfortunately, results of treatment have improved only slightly in the past 40 years, with dry (cure) rates for pharmacotherapy averaging about 20%.^{2,3} All major national and international organizations recommend behavioral therapy with biofeedback as the first step,⁴⁻⁶ since it can be as successful as pharmacotherapy^{3,7} and has no side-effects. Yet it remains underutilized because it is expensive and labor-intensive. Research to elucidate predictors of therapeutic response—and the mechanisms that mediate it—might facilitate better targeting of treatment, enhance therapeutic efficacy, and facilitate more widespread dissemination. However, the few studies that have examined physiological predictors of response have shown inconsistent results; still fewer studies have examined mediators. We therefore conducted a prospective trial of biofeedback-assisted pelvic muscle training (BFB) designed not to determine its efficacy but to identify predictors and mediators of therapeutic response.

2. Materials and Methods

Overview

Because causes of geriatric UI are multifaceted, we focused on discrete domains comprising disease severity and aspects of lower urinary tract physiology. By aggregating the many measured variables in this way, and by using an hypothesis-driven approach, we hoped to minimize the risk of finding chance associations.

Based on our clinical and urodynamic experience, likely physiological predictors and mediators were selected *a priori* and grouped into 4 domains: bladder proprioception, detrusor contractility, detrusor overactivity (DO) characteristics, and sphincter adequacy.⁸ For each domain we selected *a priori* one variable that we believed to be the most relevant (Table IV). We also developed *a priori* hypotheses for each domain (Table I).

Setting and Subjects

Community-dwelling women were recruited by newspaper ads to a research laboratory between February 2004 and April 2008. Eligibility included age > 60 years, ≥ 2 UI episodes/week for ≥ 6 months by self-report, and ≥ 1 episode on a 3-day bladder diary. We excluded those with impaired mobility or cognition (MMSE score <24/30 or inability to follow study procedures); clinically-apparent neurological lesion; prolapse beyond the hymen; interstitial cystitis; spinal cord injury; history of pelvic radiation or advanced uterine or bladder cancer; multiple sclerosis; urethral obstruction; urinary retention (PVR >200 ml after non-instrumented void); medical instability or expected medication change during the study; or any condition requiring intravenous antibacterial prophylaxis before urodynamics. Subjects gave written consent after being informed in detail about the study's goals and its potential benefit to themselves. They received modest compensation for each visit. The study was approved by the University of Pittsburgh IRB. Of note, NIH reviewers declined funding of a control group.

Evaluation

Before and after the 8–12 week intervention we obtained a medical and voiding/incontinence history and performed a physical examination (including neurological, cognitive and stress testing).⁹ Post-void residual volume (PVR) was obtained by ultrasound on at least 2 occasions within 10 minutes of a privately-performed void. Subjects completed a baseline bladder diary for 3 consecutive 24-hour periods. They recorded voiding times and volumes, and circumstances and amount of leakage; the amount was quantified as small [5 ml], moderate [15 ml], or large [60 ml], and was added to total volume voided to estimate daily output.⁸ A 24-hour pad test was performed on the third day of the diary to measure the amount of urine leaked.^{10,11}

Comprehensive videourodynamic evaluation (pre- and post-intervention) followed internationally-accepted guidelines,^{9,12,13} and aimed to reproduce the patient's symptoms. It included uroflowmetry; ultrasound PVR determination; urethral pressure profilometry at rest and during volitional squeezing of pelvic floor muscles, straining, coughing, and bulbocavernosus reflex (BCR) testing; fluoroscopically-monitored cystosphincterometry (filling rate 30 ml/min) with room-temperature fluid and simultaneous monitoring of intravesical, abdominal and maximum urethral pressures; and pressure-flow voiding studies with a stop-test to estimate isovolumetric pressure. No limit on bladder volume was imposed other than involuntary voiding or subject discomfort; bladder diary volumes were used to confirm adequate filling. If DO/UI did not occur spontaneously, we tried to provoke it with coughing, laughing, suprapubic tapping, running water, placing the hand in warm water, short periods of faster filling (60 ml/min), catheter manipulation, change of posture from supine to sitting to standing, and walking a few steps with a full bladder to a commode.

Components of the evaluation, such as urethral pressure profile (UPP) and pressure-flow study, were repeated if apparently unrepresentative. During maneuvers such as sphincter/pelvic floor squeeze the catheter displacement was monitored fluoroscopically. Cystometric capacity was determined from the final voided volume plus PVR. Methods and definitions (see Table IV) conform to ICS standards¹⁴ except for: DO velocity (max dp_{det}/dt during DO), DO amplitude ($p_{det,max}$), DECO (detrusor contraction strength coefficient),¹⁵ and squeeze pressure (maximum pressure on voluntary squeeze at BN or striated sphincter). Urodynamic testing lasted 1–2 hours in each subject.

Intervention

BFB comprised two biofeedback sessions (60–90 minutes) followed by two sessions of verbal coaching and instruction (30–45 minutes). These 4 visits were preceded and followed by visits for clinical and urodynamic assessment. Visits were nominally scheduled biweekly; for logistical reasons, the final evaluation was typically conducted 12 weeks after starting BFB. BFB followed Burgio's protocol⁷ and was administered by an experienced continence nurse practitioner (LO), trained and monitored during some studies by Dr. Burgio. Subjects were asked to practice exercises at home and keep daily bladder records. At the first session, after review of history, fluid intake, medication use, and prior experience with pelvic floor muscle training, biofeedback was explained and subjects were asked to contract the anal sphincter as if to hold back gas or stop a bowel movement. Two surface EMG electrodes

were placed on the anal verge, with a grounding electrode on the buttock and another electrode on the abdomen to determine use of accessory or gluteus muscles and hip adductors. Signals were displayed to coach subjects to use the correct muscles. Subjects were given an individualized exercise program for home practice. At the second session, bladder records were reviewed, in addition to changes in medications, medical condition, and fluid intake; and subjects were questioned about the circumstances that provoked urgency and leakage. Urge suppression strategies were introduced (relaxation at onset of urgency and quick pelvic floor muscle contractions). With biofeedback, subjects demonstrated the pelvic floor muscle exercises and received correction and encouragement. The home practice assignment included both exercises and urge suppression strategies. At session 3, urge suppression strategies were refined. At session 4, progress was reviewed, with encouragement and suggestions for improvement.

Statistical methods

All analyses described were planned *a priori* unless otherwise stipulated. Percentage reduction in incontinence episodes, recorded on a 3-day bladder diary, was defined as the primary outcome.^{7,11,16} We used 50% improvement (close to the median) as a secondary definition of responders to illustrate the results. To confirm validity we used the total pad weight gain on the pad test. *Predictors* were defined as variables whose *baseline* values correlated significantly with therapeutic response. *Mediators* were defined as variables whose *change* from baseline correlated with therapeutic response, with a direction and magnitude both statistically significant and biologically plausible. We also expected that the variables in any domain involved in prediction or mediation would show consistent directions of difference or change, thus confirming involvement of the domain as a whole.

SAS[®] version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for statistical analyses. We used quantile (median) regression,^{17,18} implemented in the SAS[®] QUANTREG procedure, to identify potential predictors and mediators. Median regression is more robust than standard least-squares regression when data are skewed, as in this study where it is possible to have an unbounded deterioration of percentage change but maximum improvement is limited to 100%. Statistical significance of the regression coefficient at the $\alpha = 0.05$ level was interpreted as evidence of a predictor's or mediator's importance. Calculations based on preliminary dichotomized data suggested that 180 subjects would yield 80% statistical power. The regression procedure used in the actual study should provide higher power.

3. Results

Of 649 subjects who responded to a newspaper advertisement, 279 appeared eligible on telephone screening and agreed to enroll; 61 either withdrew at the initial face-to-face visit ($n=32$) or were found to be ineligible ($n=29$). Of the remaining 218 subjects, 35 later withdrew: 14 owing to surgery for other conditions, 9 for intercurrent health problems, 4 who refused follow-up urodynamic study, 4 who relocated, and 4 for logistical reasons. Thus, 183 subjects aged 60–93 years completed the study. Recruitment bias was minimized by the relatively high rate of enrollment in response to advertisement ($218/649=33\%$) and

the low dropout rate (35/218=16%), which we attribute to the friendly atmosphere generated by our staff and their screening expertise.

Demographic and clinical data are presented in Tables II and III. At baseline, median UUI frequency was 3.2 episodes per day, corresponding to severe incontinence.⁷

BFB substantially reduced the frequency and amount of UUI (Table III). The percentage of responders (50% reduction in UUI frequency) was 55%; 34% of subjects achieved 75% improvement, and 13% achieved full continence. Subjects also experienced a small decrease in voiding frequency, accompanied by a parallel increase in daytime voided volume and a decrease in 24-hour excretion (Table III).

Despite extensive provocation, DO was observed in only 43% of UUI subjects during baseline urodynamics. DO characteristics could be measured only in this subgroup.

Predictors

Baseline UUI frequency predicted therapeutic response ($p=0.04$; see Figure 1). Table IV shows potential urodynamic predictors, stratified by response. One or two potential predictors in each of the 4 physiological domains were associated with therapeutic response, although none was the postulated primary variable. The difference between responders and non-responders was in the direction postulated in Table I for 3 of the 4 *a priori* postulates, albeit only minimally. Pad test measurements yielded similar results.

Specific Physiological Domains

Proprioception: None of the three standard measures of bladder sensation¹⁴ was a significant predictor (Table IV). One measure of warning – the difference between cystometric capacity and first sensation of filling – was statistically significant, but not in the direction postulated.

DO Characteristics: As postulated, more aggressive DO (higher DO velocity and amplitude) predicted poor response, although these parameters could be measured only in the 43% of subjects with DO on urodynamics. According to the adjusted regression analysis (Table IV), for each 1.5 cm H₂O/s increase in DO velocity the absolute percentage improvement decreased by 15 (e.g., from 55% to 40%), a clinically significant amount. Neither the onset volume of DO nor the detectable presence of DO was a significant predictor (e.g., 51% of those with baseline DO responded vs. 58% of those without DO, $p=0.3$).

Urethral Sphincter Adequacy: We planned to assess sphincter function by the ability to interrupt leakage during DO (“two-minute test”).¹² However, owing to the unexpectedly low prevalence of DO, we reverted to secondary measures defined *a priori*: sphincter strength at bladder neck and striated sphincter levels as assessed by volitional squeeze during filling. Only low squeeze pressure at the bladder neck significantly predicted improvement, as postulated in Table I, but not by a clinically significant amount.

Detrusor Contractility: Of the 3 measures of contractility, only low isovolumetric detrusor pressure predicted good response, consistent with our postulate. However, it could be measured only in the 93 subjects able to voluntarily interrupt voiding and, since the mean difference between responders and non-responders was only 3.6 cm H₂O, it was likely not a clinically useful predictor.

Multivariable Models—We constructed multivariable median regression models based on the 4 urodynamic variables significant in the bivariate analyses, with and without adjustment for baseline UUI frequency (results not shown). Because models that included DO characteristics and isovolumetric detrusor pressure excluded the majority of subjects, we also constructed models that omitted these variables. With either 3 or 4 independent variables in the regression, none was significant. With 2 variables in the equation, both warning from first sensation to capacity and isovolumetric detrusor pressure remained significant in some analyses, and regression coefficients were concordant with the bivariate values in Table III.

Mediators

When stratified by responder status, BFB-induced changes were significantly associated with therapeutic improvement for only two clinical parameters—voiding frequency and 24-hour fluid excretion (diuresis) (see Table V)—and one urodynamic parameter: the presence or absence of DO (see subgroups A to D in Table VI). If DO was not observed at baseline but was observed following BFB (subgroup C), then improvement was 38%, whereas if DO was present prior to BFB and disappeared after treatment (subgroup B) then therapeutic response was greater (69%). Thus, change in DO status correlated with improvement. However, response was much more strongly related to the presence of DO following treatment, regardless of its presence before therapy: those with DO after therapy were substantially less likely to have been responders. Of note, response did not correlate with change in the volume at which DO occurred, or the velocity or amplitude of DO.

For all but one of the variables in Table V, statistical significance of a potential mediator was determined by median regression and did not depend on the definition of “response” (e.g., 50% or 75%). For the presence of DO, however, median regression was not feasible and significance had to be assessed from numbers of responders. Therefore, we performed a sensitivity analysis. With response defined as >50% improvement in UUI frequency (Table VI), there were significant differences among subgroups A to D overall ($p=0.009$) and between subgroups B and C ($p=0.05$). With response defined as >75% improvement, differences were still significant overall ($p=0.03$) but not between subgroups B and C ($p=0.6$). With response defined as 100% improvement (dry), no difference was significant, likely owing to the small proportion who achieved this outcome; “dry” rates for the subgroups were 10%-20%.

Of note, there was minimal change in cystometric capacity (563 ± 190 vs. 549 ± 190 ; $p=0.2$) or urethral sphincter strength. Postulating that improved sphincter strength might be more important in subjects who had a weak sphincter prior to BFB, we stratified the data by baseline sphincter strength; results were nearly identical. We then sub-stratified these results

according to the presence or absence of DO at baseline and again found neither a statistically nor clinically-suggestive correlation with therapeutic response (results not shown).

4. Discussion

This study confirmed the efficacy of BFB for UUI in older women.^{1,2,19} The mean reduction in UUI episodes (by 1.6 per 24 h) was similar to that seen in prior studies (1.3–1.9 episodes/24 h), despite our subjects' greater age and higher baseline UUI frequency (3.6/24 h vs. 2.2–2.5/24 h).²

Predictors

Baseline UUI frequency predicted treatment success: with 2 episodes of UUI/24 hours, the chance of becoming dry on end-study evaluation was 26%; with 1 UUI episode/day the proportion was 35%. These results are similar to Burgio's for BFB⁷ and to others' for drug treatment,²⁰ and may be useful for patient counseling.

Most systematic reviews have concluded that the efficacy of behavioral and pharmacological approaches to UUI is equivalent.^{2,3,21} For cognitively-intact older adults, however, behavioral approaches are appealing because they avoid potential side effects and drug interactions. But BFB is labor-intensive, costly, requires diligent adherence and well-trained therapists and, like pharmacotherapy, has modest efficacy in restoring continence. Thus we aimed to determine whether it was possible to better target patients because there is currently no consensus.^{2,22,23} Since experience suggests that therapeutic response correlates inversely with impaired mood, mentation, and mobility,¹ we excluded such patients and instead focused on carefully measured urodynamic parameters.

For most urodynamic parameters, correlations with BFB response were not statistically significant. Even the point estimates were unimpressive, and there was little consistency between similar measures in the same domain. For instance, although one measure of proprioception (warning from first sensation to capacity) correlated significantly with outcome in the unadjusted analysis (Table IV) and survived one multivariable analysis, it was the only one of 7 variables in the domain that was statistically significant, it was in the direction opposite to that postulated, and it involved first sensation of filling, which alone was not significant and is likely the least reproducible of our proprioception measures. Similarly, for contractility, only one of three parameters (isovolumetric detrusor pressure) was significant, it barely survived multivariable analysis, and the differences between responders and non-responders was clinically unimpressive. For sphincter strength, all three measures were in the direction postulated, and one was significant, suggesting that strengthening of a weak sphincter may contribute to improvement (Table 1). However, the difference between responders and non-responders was small and clinically insignificant.

By contrast, correlations with measures of DO aggressiveness were more consistent and compelling. All four correlations were in the direction postulated (more aggressive DO = less improvement) and two were statistically significant despite the smaller number of individuals in whom DO could be elicited. Furthermore, the differences between responders and non-responders were substantial (50% vs. 90%). Unfortunately, the utility of such

parameters for predicting therapeutic response is limited owing to the small proportion of UUI patients in whom DO can be elicited during urodynamic testing and also because the overlap is large. Moreover, the mere observation of DO was not predictive of treatment outcome.

The low prevalence of elicitable DO was surprising, especially given the extensive efforts to elicit it. We believe that this reflects the situational nature of UUI in this population, which could not be reproduced in the laboratory. Situational UUI may represent one phenotype whereas UUI with severe (brisk, large-amplitude) DO may be a different phenotype that is resistant to treatment with BFB.

Mediators

The mediator analyses (Table V) indicate that successful BFB improves UUI without significantly changing mechanical properties of the bladder or urethra such as bladder capacity, proprioception, detrusor contractility, or sphincter strength. The only potential urodynamic mediator of improvement was the presence or absence of DO (Table VI). If subjects are divided into 4 subgroups based on presence or absence of DO before and after therapy, the difference between the responses in subgroups B and C suggests that DO presence is responsible for an absolute difference in improvement of roughly 30%, a clinically significant amount. Nevertheless, response is much more strongly dependent on the presence of DO at the conclusion of BFB than prior to starting BFB; roughly 40% of those with DO at conclusion of the study had responded, regardless of whether DO was present at baseline, while roughly 70% of those without DO at conclusion of the study had responded, again unrelated to the presence of DO prior to BFB. A possible reason is that the first urodynamic test (with a naïve and anxious patient) is a less reliable indicator of bladder status than the second.^{24–26}

Regardless of the presence or absence of DO at baseline, its absence among those who respond to therapy may reflect an improvement in CNS control of the bladder. Consequently, responders can void less frequently (Table V) because they feel less need for pre-emptive voiding. Goode et al reported a similar observation.²²

Interestingly, change in DO characteristics did not correlate with improvement in UUI. Although statistical power was less than anticipated owing to a lower than expected prevalence of DO, the changes observed were both statistically insignificant and opposite to the direction predicted. In the predictor analysis (Table IV) we found that UUI associated with strong and brisk DO is resistant to BFB. Thus we speculate that two factors contribute to UUI or its response to therapy: the aggressiveness (strength and briskness) of the underlying DO, and the efficiency of central (cerebral) control. The importance of these two factors may vary in different UUI phenotypes and suggest the optimum treatment: for example, behavioral therapy if impaired control predominates or anticholinergic medication if DO is aggressive.

BFB-related changes in urethral sphincter parameters were not convincing as mediators of improvement, even when stratified, suggesting that sphincter strength has little if anything to do with response to BFB for UUI.

Decreased fluid output post-intervention (Table III) presumably reflects advice about fluid intake provided during BFB training. The reduction was greater among responders than non-responders (Table V), suggesting that it may contribute to UUI improvement, albeit the decrease was small. (The coefficient of median regression indicates that for each 100 ml reduction in fluid output the absolute improvement in UUI frequency was only 2%). However, the significant increase in mean volume of each daytime void confirmed an increased tolerance of bladder filling in these patients.

It is difficult to compare our results with those of prior studies because most were small, utilized less comprehensive urodynamic assessment, and found inconsistent relationships. For example, Burgio treated 20 UUI patients with BFB and found no correlation between clinical improvement and any of the cystometric parameters examined, including bladder capacity, sensation of fullness, DO onset volume, warning from sensation of fullness until DO onset, and the strength or duration of sphincter contraction; DO persisted in almost all subjects.²⁷ In a larger group of women, change in simple cystometric parameters also showed no correlation with outcome.²⁸ By contrast, another study found that bladder capacity increased among young women who underwent BFB.^{29,30} The only study to evaluate sphincter strength found that it increased with BFB, although the authors did not examine whether the increase correlated with response.³¹ And of the four studies that assessed persistence of DO, one found that it vanished in every subject who became continent,³² while the others found that it persisted in the majority.^{22,27,30}

Strengths and Limitations—This study had several strengths, including its large size, prospective design, comprehensive videourodynamic evaluation by an experienced team, intervention by a single experienced therapist, and *a priori* defined terms, domains, and analyses.

The study also had limitations. Owing to its design, which required at least two months' participation and repeated urodynamic evaluations, only one-third of respondents to our ads elected to enroll; therefore, we cannot know how they differed from participants. Those who withdrew after enrollment, however, did not differ from the rest. Second, in the absence of a control group, we contrasted subjects with differing responses to therapy. Consequently we could not evaluate any placebo component. Yet, a placebo response is inherent to a BFB program and its impact on the results is unclear because all subjects were exposed to it equally.

Another apparent limitation was the presence of DO in <50% of subjects. This was unexpected in this elderly cohort and occurred despite detailed testing by an experienced team who employed extensive provocative maneuvers. Although the low DO prevalence reduced statistical power below the >80% calculated in advance, it is unlikely that this affected our conclusions because observed differences between responders and non-responders on nearly every postulated variable were not only insignificant but also either minimal or in a direction that was not biologically plausible. The low prevalence of DO did, however, preclude our ability to use the "two-minute test"¹² to determine whether the success of BFB is mediated by an acquired ability either to suppress the DO or to prevent the associated leakage by tightening the sphincter.

Inability to elicit DO precluded measurement of its severity, while easily elicitable DO proved to hinder an adequate stop test, preventing measurement of isovolumetric detrusor pressure in 49% of subjects. In addition, some subjects with DO reported first desire to void as their earliest sensation during filling cystometry. Consequently first sensation of filling was absent in 25% of subjects. These “missing” values are unavoidable in this patient population and indeed provide further information about it. Nevertheless they limited the utility of multivariable regression analyses.

5. Conclusions

Baseline UII frequency predicts response to BFB, implying that BFB might be the first-line treatment for functionally and cognitively intact older women with mild to moderate UII, while pharmacological therapy may be better for those with severe UII. Beyond this—and despite the study’s prospective nature, relatively large size, multidimensional urodynamic evaluation, and *a priori* specified hypotheses and subanalyses—the only urodynamic parameters that emerged as clinically convincing predictors of therapeutic response were related to DO severity, and even these are likely of little utility in clinical practice.

Nonetheless, the predictor analysis shows that the severity of DO augurs resistance to BFB. This suggests that characteristics of DO may be important in defining phenotypes and the mechanisms mediating therapeutic response. The mediator analysis corroborates this conclusion: the efficacy of BFB for UII appears to be mediated by changes in the elicibility of DO, suggesting that its mechanism relates more to enhancing central control of the bladder than to an impact on mechanical properties of the bladder or urethra. Because the severity of DO predicts resistance to BFB, DO may exist as at least two phenotypes, each of which may warrant a different initial therapeutic approach.

The fact that this study was largely negative does not detract from its significance. Given its size, design, and detailed urodynamic methodology, it establishes definitively that there are few useful predictors or mediators of improvement with biofeedback, a clinically and scientifically significant conclusion.

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Fig. 1. Effect of baseline frequency of UUI episodes on the chance of becoming dry after treatment (significant, $p < 0.01$)

With less than 2 episodes of UUI per 24 hours at baseline, the chance of becoming dry was 26%. With 4 or more episodes per 24 hours, the chance of becoming dry was only 4%. If baseline frequency was less than one per 24 hours then chance of becoming dry was 35% (not shown).

Table I*A Priori* Specified Postulates Regarding Predictors and Mediators, Domains and Rationale

Domain and Postulate: Predictors	Rationale
Proprioception: BFB will be more effective among those with less warning of UUI.	Briefer warning increases the likelihood that DO (regardless of whether demonstrated urodynamically) will result in UUI. BFB may improve proprioception or teach patients with impaired warning ways to adapt to it.
DO Characteristics: Subjects with more severe DO, as assessed by DO velocity, amplitude and onset volume, will be more resistant to BFB.	Severe DO will be more refractory to therapy.
Sphincter strength: BFB will be less effective for patients who already have a strong sphincter.*	Many older patients have weak sphincters, which may increase the likelihood of UUI if DO is also present. Those whose UUI occurs despite normal sphincter strength would be less likely to improve with BFB than would those with a weak sphincter (provided that innervation is intact).
Detrusor Contractility: Those with weaker bladders will respond better to BFB.	BFB tries to teach patients how to suppress detrusor contraction and how to improve sphincter adequacy. These efforts should be more successful in patients with weaker bladders.
Domain and Postulate: Mediators	Rationale
Fluid excretion. Recorded 24- hour fluid excretion (on the bladder diary) will decrease in responders	Responders will learn to restrict fluid intake to reduce UUI
DO severity —as assessed by DO velocity, amplitude, and onset volume—will become less severe in responders	Responders will learn through BFB to moderate DO severity by increasing onset volume and decreasing DO velocity and amplitude
Sphincter adequacy. Timing of sphincter contraction to inhibit DO (the two-minute test) will improve in responders. Alternatively, urethral pressure and squeeze pressure will increase in responders	Responders will improve sphincter control and strength
Proprioception. Warning (volume at DO onset [†] minus volume at first desire to void) will increase in responders	BFB may improve proprioception, thus increasing warning time and reducing likelihood of UUI

* Logistical reasons precluded the planned assessment of appropriate timing of the sphincter contraction.¹²

Table II

Demographic and Clinical Characteristics of the Study Sample at Baseline

N	183
Age (years, mean $\pm$ SD)	73.6 $\pm$ 7.6
Mini-Mental State Exam (MMSE)/30 (mean $\pm$ SD)	29.2 $\pm$ 1.3
Independent in all IADLs and fully mobile	100%
Anticholinergic drug for UII in the past	36%
Anticholinergic drug for UII currently	4%
History of depression (none currently active)	30%
Diabetes mellitus	11%
Stroke by history (more than 1 year ago)	6%
Hysterectomy	47%

Selected Incontinence and Voiding Parameters of the Study Sample Before and After BFB Intervention

Table III

	Pre-intervention		Post-intervention		p-value of difference in means
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Incontinence frequency (#/24h)	3.6±2.4	3.2 (0.3–11.3)	2.0±2.3	1 (0–10)	0.0001
Urine loss (grams/24h)	99±164	36 (4–1025)	55±117	5 (0–667)	0.0001
Voiding frequency (#/24h)	8.7±2.7	8.4 (3–21)	7.7±1.8	7.7 (3–13)	0.0001
Diuresis (ml/24h) *	1861±738	1758 (604–5039)	1750±711	1651 (410–4024)	0.004
Volume per daytime void (ml)	179±83	150 (50–465)	196±90	180 (45–480)	0.0002

* Includes measured voids and imputed leakage volumes; see text

Table IV

Urodynamic Domains and Potential Predictors

Relationship between improvement and potential physiological (urodynamic) predictors, based on median regression analyses (unadjusted and adjusted for baseline incontinence frequency). Results of adjusting for confounders are shown in the footnotes. Mean values of potential predictors are also shown, stratified by response to therapy. To illustrate how such data can be used, if warning is defined as the volume between first sensation and cystometric capacity, then the predictor unit is 41 ml (far right column) and the unadjusted regression coefficient is 3. Thus, for each 41 ml increase in warning, the percentage improvement increases by 3 (e.g., from 50% to 53%). Such a small improvement would not be clinically significant, even though the regression coefficient is statistically significant ($p = 0.05$).

URODYNAMIC DOMAINS and variables * =variable selected <i>a priori</i> to represent the domain	Unadjusted for pre-intervention UUI frequency			Adjusted for pre-intervention UUI frequency			Responders Pre-intervention mean $\pm$ standard deviation	Non-responder Pre-intervention mean $\pm$ standard deviation	Predictor unit [‡] used for regression coefficient computation
	Median regression coefficient $\pm$ standard error		p	Median regression coefficient $\pm$ standard error		p			
	raw	in predictor units [‡]		raw	in predictor units [‡]				
PROPRIOCEPTION									
First sensation of filling (ml)	0.036 $\pm$ 0.050	0.7	0.47	0.021 $\pm$ 0.046	0.4	0.66	217 $\pm$ 102	198 $\pm$ 114	19
First desire to void (ml)	0.031 $\pm$ 0.034	0.6	0.37	0.017 $\pm$ 0.033	0.3	0.60	295 $\pm$ 126	276 $\pm$ 136	19
Strong desire to void (ml)	0.014 $\pm$ 0.027	0.3	0.61	0.014 $\pm$ 0.022	0.3	0.51	412 $\pm$ 168	393 $\pm$ 174	19
Warning, 1 st sensation to capacity (ml)	0.068 $\pm$0.034	3	0.05	0.064 $\pm$ 0.035	3	0.07 ¹	392$\pm$137	351$\pm$188	41
Warning, 1 st desire to capacity (ml)	0.059 $\pm$ 0.043	0.9	0.17	0.030 $\pm$ 0.038	0.4	0.44	288 $\pm$ 117	273 $\pm$ 165	15
Warning, strong desire to capacity (ml)	0.036 $\pm$ 0.037	0.1	0.33	0.014 $\pm$ 0.032	0.1	0.67	163 $\pm$ 137	159 $\pm$ 145	4
Warning, first desire to DO onset (ml) *	0.020 $\pm$ 0.073	0.1	0.78	-0.006 $\pm$ 0.063	-0.03	0.93	130 $\pm$ 36	125 $\pm$ 103	5
DO CHARACTERISTICS									
DO presence (0 or 1)	-4.25 $\pm$ 9.9	-4	0.67	-5.10 $\pm$ 7.89	-5	0.52	0.40	0.46	1
DO velocity (cm H ₂ O/s)	-10.8 $\pm$3.9	-16	.007	-9.80 $\pm$4.49	-15	0.03²	1.64$\pm$1.14	3.15$\pm$2.91	1.5
DO amplitude (cm H ₂ O)	-0.95 $\pm$0.47	-9	0.05	-0.83 $\pm$ 0.47	-8	0.08 ³	19.5$\pm$12.7	29.4$\pm$25.1	9.9
DO onset volume (ml) *	0.045 $\pm$ 0.040	3	0.27	0.013 $\pm$ 0.044	0.8	0.77	389 $\pm$ 187	331 $\pm$ 166	58
URETHRAL SPHINCTER ADEQUACY									
MUCP (cm H ₂ O)	-0.32 $\pm$ 0.27	-1	0.24	-0.40 $\pm$ 0.25	-1	0.11	49.3 $\pm$ 17.6	52.9 $\pm$ 25.3	3.6

URODYNAMIC DOMAINS and variables * =variable selected <i>a priori</i> to represent the domain	Unadjusted for pre-intervention UUI frequency		Adjusted for pre-intervention UUI frequency			Responders	Non-res ponders	Predictor unit [‡] used for regression coefficient computation	
	Median regression coefficient ± standard error		p	Median regression coefficient ± standard error		p	Pre-intervention mean ± standard deviation		
	raw	in predictor units [‡]		raw	in predictor units [‡]				
Squeeze pressure, BN (cm H ₂ O)	-0.48 ±0.24	-3	0.05	-0.39 ±0.25	-2	0.11	23.3±16.9	29.1±21.0	5.8
Squeeze pressure, striated sphincter (cm H ₂ O) *	-0.19 ±0.33	-0.4	0.57	-0.098 ±0.31	-0.2	0.75	26.7±17.7	28.8±19.7	2.1
DETRUSOR CONTRACTILITY									
PVR (ml)	-0.011 ±0.042	-0.1	0.79	-0.0003 ±0.039	-0.002	0.99	61.9±113	54.9±88.9	7.0
DECO contraction strength coefficient *	0.042 ±0.13	0.04	0.74	0.080 ±0.11	0.1	0.49	103±40	102±42	1
Peak isovol pressure (cm H ₂ O)	-0.92 ±0.43	-3	0.03	-0.86 ±0.42	-3	0.04 [‡]	27.6±11.9	31.2±12.8	3.6

* = variable selected *a priori* to best represent each domain **Bold** = significant association with improvement (p < 0.05)

[‡] Unit used for displaying regression coefficient in columns 3 and 6 represents the difference between mean baseline values in responders and non-responders; for DO, the value is 1 if DO was observed and 0 if it was not.

¹ p < 0.05 after adjustment for pre-intervention severity, age and MMSE score

² p < 0.005 after adjustment for pre-intervention severity, age and MMSE score

³ p < 0.01 after adjustment for pre-intervention severity, age and MMSE score

⁴ p < 0.05 after adjustment for pre-intervention severity, age and MMSE score

Table V
Relationship Between Potential Mediators and Improvement, Using Median Regression (Adjusted for Baseline Incontinence Frequency)

Also shown, for illustrative purposes, are the mean values, as well as the difference in the means, before and after therapy, stratified by responder/non-responder status.

		Responders n=100 ‡				Non-responders n=83 ‡			
		p	pre	post	post-pre	pre	post	post-pre	
DOMAINS and variables in regression equation									
	Median regression coefficient adjusted								
PROPRIOCEPTION									
First sensation of filling (ml)	-0.030 ±0.040	0.45	217 ±102	212 ±95	-5 n=67	198 ±114	210 ±109	2 n=50	
First desire to void (ml)	0.057 ±0.033	0.08	295 ±126	336 ±148	43	276 ±136	293 ±150	17	
Strong desire to void (ml)	0.027 ±0.034	0.43	412 ±168	443 ±169	31	393 ±174	406 ±188	13	
Warning, 1 st desire to capacity (ml)	-0.013 ±0.027	0.63	288 ±117	230 ±152	-58	273 ±165	247 ±138	-26	
Warning, 1 st sensation to capacity (ml)	0.016 ±0.032	0.61	392 ±137	356 ±172	-36 n=65	351 ±188	324 ±172	-27 n=50	
Warning, strong desire to capacity (ml)	0.001 ±0.022	0.96	163 ±137	115 ±142	-48	159 ±145	127 ±134	-32	
warning 1 st desire to DO onset (ml) *	0.002 ±0.097	0.98	139 ±136	137 ±184	-2 n=19	125 ±103	158 ±131	33 n=23	
DO CHARACTERISTICS									
DO velocity (cm H ₂ O/s)	5.6 ±4.9	0.26	1.64 ±1.14	2.26 ±1.77	0.62 n=20	3.15 ±2.91	2.82 ±2.81	-0.33 n=27	
DO amplitude (cm H ₂ O)	0.40 ±0.70	0.57	19.5 ±12.7	18.2 ±8.1	-1.3 n=21	29.4 ±25.1	24.4 ±12.9	-5 n=27	
DO, onset volume (ml) *	-0.043 ±0.057	0.45	389 ±187	392 ±212	3 n=21	331 ±166	402 ±203	71 n=27	
URETHRAL SPHINCTER									
MUCP (cm H ₂ O)	-0.039 ±0.35	0.91	49.3 ±17.6	49.4 ±18.9	0.1	52.9 ±25.3	53.0 ±24.9	0.1	
Squeeze pressure, BN (cm H ₂ O)	0.42 ±0.29	0.15	23.3 ±16.9	24.3 ±15.2	1	29.1 ±21.0	25.6 ±18.0	-4	
Squeeze pressure, striated sphincter *	0.12 ±0.26	0.63	26.7 ±17.7	24.8 ±17.2	2 n=77	28.8 ±19.7	26.3 ±16.4	-3 n=62	
DETRUSOR CONTRACTILITY									
PVR (ml)	-0.001 ±0.026	0.96	62 ±113	59 ±98	-3	55 ±89	62 ±109	7	
DECO contraction strength coefficient *	-0.25 ±0.14	0.08	103 ±40	101 ±38	-2 n=86	102 ±42	99 ±38	-3 n=68	
Peak isovolumetric pressure (cm H ₂ O)	-0.093 ±0.59	0.87	28 ±11.9	28 ±13	0 n=36	31.2 ±12.8	33.0 ±14	2 n=22	

			Responders n=100 [‡]			Non-responders n=83 [‡]			
DOMAINS and variables in regression equation	Median regression coefficient adjusted	p	pre	post	post- pre	pre	post	post- pre	
CLINICAL DOMAINS									
24-h voiding frequency	-3.63 ± 1.90	0.06	8.9 ± 3.0	7.4 ± 1.7	-1.5	8.5 ± 2.3	8.0 ± 1.9	-0.5	
24-h voided volume (ml) [*]	-0.020 ± 0.009	0.02	1876 ± 702	1769 ± 704	-107	1747 ± 780	1677 ± 719	-70	
24-h diuresis (ml/24 h)	-0.021 ± 0.008	0.01	1908 ± 703	1776 ± 707	-132	1803 ± 779	1713 ± 716	-90	

‡ Total number of responders and non-responders. Numbers of subjects (n) in individual comparisons are all at least 90% of this total except where explicitly noted. For explanation of missing values see text.

* Variable postulated a priori to best represent each domain.

Table VI

DO Presence Before and After Intervention

DO presence	pre post		n	Median % improvement	Responders [‡]	Significance
subgroup A	no DO	no DO	79/183	67%	50/79 = 63%	for A to D $\chi^2 = 11.5$ p<0.01 for B vs C $\chi^2 = 4.9$ p<0.05
subgroup B	DO	no DO	27/183	69%	19/27 = 70%	
subgroup C	no DO	DO	25/183	38%	10/25 = 40%	
subgroup D	DO	DO	52/183	43%	21/52 = 40%	

[‡]Percent of subjects within each subgroup who were responders to B