Detrol Long Acting (LA) vs Estrace Vaginal Cream for the Treatment of Overactive Bladder Symptoms (DRIVE)

Study Protocol and Statistical Analysis Plan

NCT00465894

July 30, 2018

Kimberly A. Gerten, M.D., Principal Investigator

University of Alabama at Birmingham

Birmingham, AL 35294

Clinical Study Proposal

Randomized controlled trial of Tolterodine versus low-dose intra-vaginal estradiol cream for the treatment of overactive bladder in post-menopausal women.

Kimberly A. Gerten, M.D. and Holly E. Richter, PhD, M.D.
University of Alabama at Birmingham

Aims:

Primary

1. To determine if long acting tolterodine confers more benefit than intra-vaginal low dose estrogen in the treatment of Overactive Bladder Syndrome at twelve weeks post treatment initiation.

Secondary

1. To determine if patients with subjectively unsatisfactory results with monotherapy (tolterodine or estrogen cream) receive further improvement in OAB symptoms with a change to combination therapy (tolterodine plus estrogen).
2. To compare symptom specific and general quality of life and patient satisfaction measures in women treated with oral anti-muscarinic therapy versus those treated with intra-vaginal estrogen versus those treated with both.
3. To describe any change in urinary frequency or leakage in the treatment groups on a 3-day bladder diary.
4. To describe any association of symptom improvement with changes in vaginal epithelial maturation assessment.
5. To compare voiding and post micturition symptoms including slow stream, hesitancy, straining, terminal dribble, and feeling of incomplete emptying in the treatment groups.
6. To correlate observed changes in symptoms of stress incontinence in the women in each treatment group.

Relevance:

Lower urinary tract bladder storage symptoms include urinary frequency, urinary urgency, nocturia and urge incontinence. Overactive bladder syndrome is a condition in which urgency is the predominant symptom with or without urge incontinence and is usually accompanied by frequency and nocturia, as defined by the International Continence Society.[1] These are distressing problems that have a major impact on quality of life.[2] Prevalence of overactive bladder symptoms in women in the United States has been estimated to be 16-17%,[3] and this prevalence increases with age.[4, 5]

The mainstay of treatment of women with OAB syndrome is pharmacotherapy with anticholinergic agents, as well as behavioral therapy.[4, 6] Anticholinergic agents are thought to exert their effect via antagonism of the muscarinic receptors of the detrusor muscle, thus blocking transmission of the parasympathetic nervous system with subsequent reduction in detrusor muscle contraction. This method of treatment has demonstrated a 60% response rate as reported in the Cochrane Database of Systemic Reviews.[7] In addition to anticholinergic therapy, vaginal atrophy is often corrected as part of a pharmacologic treatment plan.

Vaginal atrophy is a condition that is vastly prevalent in post-menopausal women. It is thought to affect up to 48% of post-menopausal women.[8] Many women with this condition experience vaginal dryness, irritation, dyspareunia, as well as urinary symptoms including

dysuria, urgency, frequency, nocturia, incontinence and recurrent urinary tract infections.[9] Often these symptoms are dismissed as "nuisance" symptoms and treatment of atrophy is not initiated. With the waning levels of estrogen in the post-menopausal period the lower genital and urinary tracts experience thinning of the epithelium, loss of rugation, and reduced secretions.[8] Atrophy results in elevated vaginal pH, changes in the usual urogenital flora, an increased risk of urinary tract infections, as well as loss of maturation of the vaginal epithelial cells.[10]

Symptoms of urogenital atrophy may be improved with exogenous estrogen therapy. Mettler et al. demonstrated effective relief of post-menopausal atrophy symptoms using 25 micrograms of 17-β-estradiol vaginally administered tablets twice per week. Endometrial evaluation pre and post treatment showed no neoplastic findings up to 2 years after induction of therapy.[11]

Several studies have evaluated the role of estrogen in the treatment incontinence, as well as the treatment of OAB. The lower urinary tract shares common embryologic origin with the lower genital tract, and has been found to contain abundant estrogen receptors. Thus, hormonal treatment is expected to have an effect on urinary tissue, symptoms and function.[12] Estrogen therapy has shown varying results on urinary symptoms, depending on the dose and route of administration of the estrogen as well as the type of pre-treatment symptoms.

Historical studies such as a 1941 study by Salmon et. al. showed improvement in urinary symptoms in 13 of 16 women who demonstrated vaginal atrophy and had lower urinary tract complaints that were treated with intra-muscular estradiol. These authors demonstrated that symptom improvement mirrored maturation of the vaginal epithelium induced by the estrogen therapy.[13] In 1978, Walter et. al. showed a statistically significant decrease in frequency, urge, and urge urinary incontinence in a placebo controlled trial of 29 women treated with oral estradiol and estriol versus placebo. The finding of urge urinary incontinence resolved in 7 of 11 women in the active treatment group versus only 1 of 10 in the control group.[14] Two years later, Samsioe et. al. showed that 3 mg of oral estriol produced substantial improvement in urge urinary incontinence in 34 women and was significantly better than placebo in a double blind cross-over designed study.[15]

More recently, Cardozo et. al. demonstrated in a randomized controlled trial, using oral estriol given for 12 weeks, subjective and objective improvement in urgency and nocturia, but neither treatment group had statistical significance over placebo.[16] Fantl et. al. in a randomized controlled trial failed to demonstrate an effect on either objective or subjective urinary outcomes in patients treated with 3 cycles of oral estrogen.[17] In a descriptive study by the same author, less nocturia and a higher percentage of positive bulbocavernosus reflexes in women treated with estrogen supplementation was found, suggesting a lower sensory threshold in estrogen treated subjects.[18] Rufford et. al. performed a placebo controlled trial of estradiol subcutaneous implants for treatment of the urge syndrome. Subjective urgency improved in both the active and placebo groups, whereas urge incontinence improved only in the active treatment group. Adverse events (vaginal bleeding) prohibited the authors from fulfilling their enrollment goals and thus possibly failing to see further differences in treatment groups.[19]

More pertinent to our proposal are studies that employed local vaginal estrogen therapy for the treatment of lower urinary tract symptoms. Cardozo et. al. performed a double blind placebo controlled study of 110 women using vaginal estradiol tablets for the treatment of lower urinary tract symptoms. They found a statistically significant decrease in urinary urge in the active treatment group that had demonstrated pre-treatment sensory urgency.[20] Lose et. al performed a 24 week study comparing the estriol vaginal ring versus the estriol pessary. With the primary outcome being subjective questionnaire data, they

demonstrated an approximate 50% reduction in bothersome lower urinary tract symptoms. This study was limited by lack of a placebo treatment arm.[21]

In 2004, Cardozo et. al. performed a meta-analysis examining the effect of estrogen for the treatment of symptoms suggestive of overactive bladder. Local vaginal therapy was associated with a statistically significant improvement in frequency, nocturia, urgency, incontinence, bladder capacity, and first sensation to void.[22] Zullo et. al demonstrated prevention of post-operative de-novo overactive bladder symptoms in women treated with vaginal estriol ovules after placement of a TVT suburethral sling for stress urinary incontinence. Women treated with post-operative vaginal estrogen therapy had a baseline urinary urgency rate of 7%; 6 months after surgery, the rate was 4%. Women not treated with post-operative vaginal estrogen therapy had a baseline rate of urinary urgency of 7%, and, 6 months after surgery, it increased to 29%.[23]

The potential theories of why estrogen therapy may improve the symptoms of overactive bladder include increasing the sensory threshold of the bladder [18], increasing alpha-adrenergic receptor sensitivity in the urethral smooth muscle,[24] promoting beta 3 adreno-receptor mediated relaxation of the detrusor muscle,[25] and improving collagen quality and production in the peri-vesical and peri-urethral areas.[23]

No studies have been conducted looking at the treatment of storage or overactive bladder symptoms using low dose local vaginal estrogen cream in comparison to anti-cholinergic therapy, and further, whether step-wise combination treatment confers superior symptom improvement than with anti-cholinergic or estrogen therapy alone. We also wish to compare the symptoms of stress incontinence and voiding dysfunction in these subjects.

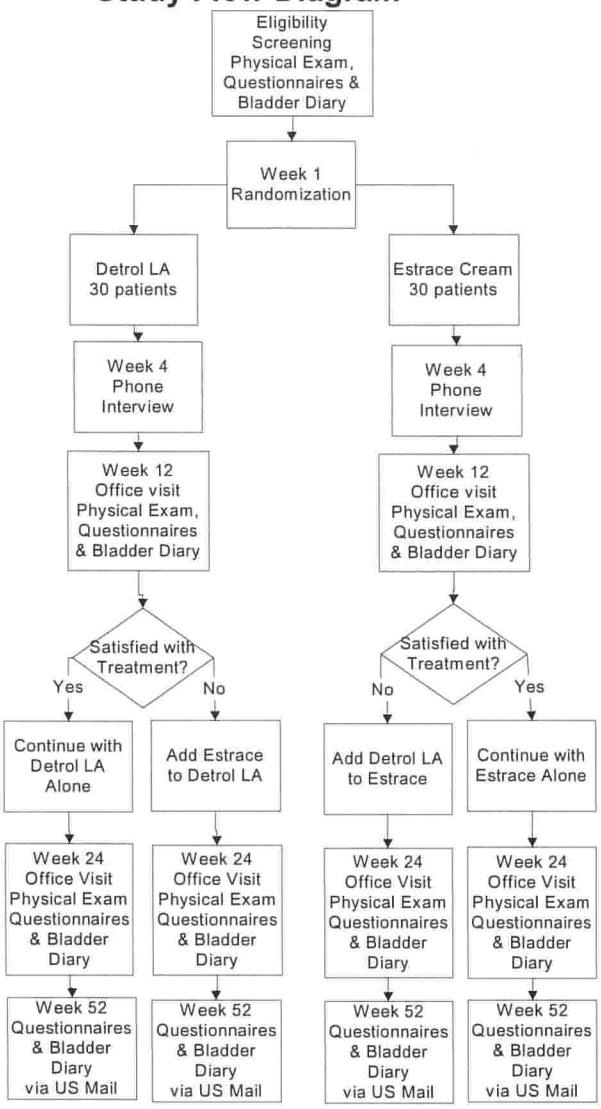
Research Design:

The study design is a randomized controlled intent to treat trial where postmenopausal women seeking care for symptoms suggestive of OAB (urgency, frequency, urge incontinence, nocturia) would be randomized to treatment with Detrol LA in study arm #1, versus treatment with local estradiol vaginal cream (Estrace,*Warner Chilcott, Rockaway, NJ*) in study arm #2. After screening for inclusion and exclusion criteria (see list below) women would be randomly assigned to a treatment group. After 12 weeks of treatment the subjects who are not completely satisfied with the results of their current therapy will be offered the opportunity to add the other therapy to their treatment regimen (see study flow diagram below). All subjects will be followed for 52 weeks. In addition to being analyzed as part of their original randomized arm, patients who receive dual therapy will be sub-analyzed for further improvement in their OAB symptoms.

Methodology/ Protocol:

Subjects will be recruited from the principal investigator's clinics as well as the Kirklin Clinic Urology clinic. Advertisements in the newspaper will also be used to recruit subjects. Patients will be screened using the OAB-q Short Form Questionnaire and the Medical, Epidemiological, and Social Aspects of Aging Questionnaire (MESA).[26] Patients will qualify with any response of "Quite a bit" or greater on the OAB-q SF questionnaire. Stratified randomization will be based on the presence or absence of SUI as demonstrated on the MESA questionnaire. The subject will then undergo a physical examination and vaginal smear.

Study Flow Diagram



Inclusion Criteria:

- Irritative voiding symptoms to include sensory urgency, frequency, urge incontinence, nocturia
- Postmenopausal women with a prior oophorectomy or 1 year from last menstrual period
- Women age 40 – 90
- *Women with hysterectomy with preserved ovaries must be age 55 or greater or have a documented FSH > 40 (to ensure post-menopausal status)
- Community dwelling
- Ability to participate in a 12 month study
- ambulatory

Exclusion Criteria:

- Post void residual > 150 ml
- Glaucoma without ophthalmologist clearance
- HRT in the past 6 months
- Current anticholinergic treatment
- Breast cancer
- Impaired mental status
- Undiagnosed vaginal bleeding in past 12 months
- endometrial thickness on pelvic ultrasound > 5 mm
- History of thromboembolic event
- Gynecologic cancer
- Untreated urinary tract infection (would be eligible after treatment)
- Stage III pelvic organ prolapse or greater
- Recent diuretic medication changes (one month from change)
- Neurologic condition affecting bladder function (Multiple Sclerosis, Parkinsons, spinal cord injury, spina bifida)
- congestive heart failure
- prior pelvic irradiation
- interstitial cystitis

Baseline measurements will include lab findings (dip urinalysis, vaginal pH, vaginal maturation index), pelvic organ prolapse quantification evaluation, subjective assessment of vaginal atrophy, a post-void residual volume and a 3-day bladder diary. Women with an intact uterus will undergo a pelvic ultrasound to assess endometrial thickness at baseline and after 12 weeks treatment with estradiol. If they do not receive estradiol treatment no follow-up ultrasound will be performed. Questionnaires include the Overactive Bladder Questionnaire (OAB-q)[27], Pelvic Floor Distress Inventory (PFDI-20), Pelvic Floor Impact Questionnaire (PFIQ-7), Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire(PISQ-12) and the SF-12, a short form general health inventory.

Detrol LA will be prescribed with a 4 mg dose QD. Estrace vaginal cream (0.1 mg estradiol per gram) will be prescribed as 0.5 grams (a finger tip length of cream) to be

applied into the vagina nightly for six weeks, then twice per week for the duration of the study (12 months).

All subjects will be called at 4 weeks to monitor for side effects and for possible drug dosage adjustment. This will be accomplished using a standardized evaluation tool.

Subjects will then be seen at 12 weeks (primary outcome visit) where a physical examination will be performed and the indices collected at baseline as well as the study questionnaires and bladder diary will be repeated. Participants that are not completely satisfied with the outcome of their current treatment regimen will be offered the opportunity to add the other therapy to their regimen. This will be determined using the Patient Satisfaction Questionnaire (PSQ) and the Patient Global Impression of Improvement (PGII). Women who where administered estradiol and have an intact uterus will undergo a pelvic ultrasound to document no change in endometrial thickness after 12 weeks of therapy.

All patients will be seen at 24 weeks for an additional physical examination to repeat baseline indices, as well as the study questionnaires and the 3-day bladder diary. Women with an intact uterus who chose to add estradiol to their treatment regimen after the 12 week visit, will undergo a pelvic ultrasound to document t no change in endometrial thickness after 12 weeks of estradiol therapy.

Finally, at 52 weeks, patients will be asked to complete an additional 3-day bladder diary, repeat the questionnaires and report their long-term management choice for treatment of their urinary symptoms via US mail.

The ultimate measure of treatment success and likelihood of long-term compliance is intrinsically linked to the patient's perception of efficacy and symptom relief. Furthermore, it is difficult to measure objective improvement in a condition like OAB were symptoms are solely subjective. Thus, the primary study outcome to be measured is subjective patient improvement in irritative urinary symptoms. The measurement tool chosen is the Overactive Bladder Questionnaire (OAB-q).[27] This instrument was chosen because it has been found to be a sensitive and reliable measure of subjective urinary symptom improvement with treatment.[31] The OAB-q is a 33-item questionnaire that has a symptom bother scale as well as a health related quality of life scale that addresses coping, concern and worry, sleep and social interaction.

Changes in urinary frequency and incontinent episodes will be documented with a 3-day bladder diary. Assessment of the subjective (atrophy assessment) and the objective (pH, maturation index) vaginal environment will be conducted by a blinded clinician. Symptoms of voiding dysfunction and stress leakage will be collected with the validated questionnaires.

Statistics:

Sample size calculation is based on a power ($1 - \beta$) of 80% and an α of 0.05. Comparison between the two groups on the validated Overactive Bladder Questionnaire (OAB-q) is the primary outcome and is, therefore, the basis of the sample size calculation. A standard deviation of 25 for this instrument was abstracted from the Coyne paper that measured the responsiveness of the instrument to anticholinergic therapy.[27] We feel that a 20 point difference in outcome on this instrument would be clinically significant because, on average, 20 was associated with a reduction of 3 or more micturations per day.[31] From these values and the proposed use of an independent t-test, 25 individuals per group were calculated. To this number, five patients per group were added to allow for attrition and intent to treat. Thus a total of 60 participants will be required to complete the study.

For the 2 groups of subjects who elect to crossover into combination therapy (i.e. Group 1 - estrogen with tolterodine added and Group 2 - tolterodine with estrogen added),

within group analyses will be performed using nonparametric testing because of the anticipated small number of subjects to crossover into combination therapy.

Timeline:

A *potential* difficulty in performing this study is subject recruitment. However, we have had success in fulfilling recruitment goals, and even exceeding them, in other recent studies addressing OAB at our institution. Our recruitment techniques are outlined under the methodology/protocol section. The following is the timeline for our study:
January 2007 Start Recruitment (Enrollment goal of 2 participants per week)
January 2008 Complete enrollment
April 2008 Publish 12 week treatment findings (Primary outcome)
Continue to collect 24 week and 52 week data
January 2009 Publish long-term treatment findings (Secondary outcome)

Relevant Prior Work:

The investigators for this proposal, *Randomized controlled trial of tolterodine versus low dose intra-vaginal estradiol cream for the treatment of overactive bladder in postmenopausal women*, are experienced in research regarding vaginal atrophy and overactive bladder (OAB) symptoms. Their research efforts are germane to this grant application and demonstrate their ability to successfully complete this project. In fact, the senior researcher Holly E. Richter PhD., M.D. has vast experience in research of OAB symptoms, even at the national multi-center level.

Dr. Richter serves as principal investigator for the Urinary Incontinence Treatment Network (UITN), which is a part of the NIH initiative to research urinary incontinence through the NIDDK, at the University of Alabama at Birmingham (UAB). Dr. Richter is currently conducting the Behavior Enhances Drug Reduction of Incontinence (BEDRI) study. The primary aim of BEDRI is to test if the addition of behavioral treatment to drug therapy (long acting tolterodine) for the treatment of urge incontinence will increase the number of patients who can discontinue drug therapy and sustain a significant reduction in incontinence. Of note, UAB exceeded enrollment expectations, and had the highest enrollment of all the involved research centers.

Other current research projects include the Weight Reduction for Incontinence Network, which is designed to determine if behavioral weight reduction results in fewer incontinence episodes, and the Incontinence Reduction After Bariatric Surgery study.

In addition Dr. Richter has successfully completed OAB related research. The Diagnostic Aspects of Incontinence Study (DAISY), which compared the accuracy of two incontinence questions to an extended questionnaire for the diagnosis of urge incontinence, recently completed enrollment. Dr. Richter also co-authored "Behavorial training with and without biofeedback in the treatment of urge incontinence in older women," which was published in JAMA in 2002, and "Predictors of outcome in the behavioral treatment of urinary incontinence in women."

Through Dr. Richter's guidance, urogynecology fellow, Thomas L. Wheeler II, M.D. has started a funded research project examining local vaginal changes (hormone receptors, markers of oxidative tissue damage and gene expression) to low dose intravaginal estradiol cream in postmenopausal women with vaginal atrophy. This project also aims to demonstrate no increased systemic estrogen activity (i.e. all forms of estrogen) in response to low dose intra-vaginal estrogen.

Clearly, Kimberly A. Gerten, M.D. is in the perfect environment to complete this proposed study. The infrastructure is in place, along with experience in completing high

level research in OAB symptoms, to support her proposal. Through Dr Richter's mentoring of Dr Gerten, the tradition of research achievement at UAB will continue.

References:

1. ABRAMS P, CARDOZO L, FALL M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. American Journal of Obstetrics & Gynecology 2002;187:116-26.
2. JACKSON RA, VITTINGHOFF E, KANAYA AM, et al. Urinary incontinence in elderly women: findings from the Health, Aging, and Body Composition Study. Obstet Gynecol 2004;104:301-7.
3. DIOKNO AC, BROCK BM, BROWN MB, HERZOG AR. Prevalence of urinary incontinence and other urological symptoms in the noninstitutionalized elderly. J Urol 1986;136:1022-5.
4. ROVNER ES, GOMES CM, TRIGO-ROCHA FE, ARAP S, WEIN AJ. Evaluation and treatment of the overactive bladder. Rev Hosp Clin Fac Med Sao Paulo 2002;57:39-48.
5. BROWN JS, GRADY D, OUSLANDER JG, HERZOG AR, VARNER RE, POSNER SF. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. Obstet Gynecol 1999;94:66-70.
6. BURGIO KL, LOCHER JL, GOODE PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. Jama 1998;280:1995-2000.
7. HAY-SMITH J, HERBISON P, ELLIS G, MOORE K. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Database Syst Rev 2002:CD003781.
8. IOSIF CS, BEKASSY Z. Prevalence of genito-urinary symptoms in the late menopause. Acta Obstet Gynecol Scand 1984;63:257-60.
9. SUCKLING J, LETHABY A, KENNEDY R. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database Syst Rev 2003:CD001500.
10. CASTELO-BRANCO C, CANCELO MJ, VILLERO J, NOHALES F, JULIA MD. Management of post-menopausal vaginal atrophy and atrophic vaginitis. Maturitas 2005;52S1:46-52.
11. METTLER L, OLSEN PG. Long-term treatment of atrophic vaginitis with low-dose oestradiol vaginal tablets. Maturitas 1991;14:23-31.
12. IOSIF CS, BATRA S, EK A, ASTEDT B. Estrogen receptors in the human female lower uninary tract. Am J Obstet Gynecol 1981;141:817-20.
13. SALMON U, WALTER RI, GEIST, SH. The use of estrogens in the treatment of dysuria and incontinence in postmenopausal women. Am J Obstet Gynecol 1941;42:834.
14. WALTER S, WOLF, H., BARLEBO, H. Urinary incontinence in postmenopausal women treated with oestrogens: a double blind clinical trial. Urol Int 1978;33:135.
15. SAMSIOE GJ, I. Urinary Incontinence in 75-year-old women. Effects of estriol. Acta Obstet Gynecol Scand 1980;97:57.
16. CARDOZO L, REKERS H, TAPP A, et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. Maturitas 1993;18:47-53.
17. FANTL JA, BUMP RC, ROBINSON D, MCCLISH DK, WYMAN JF. Efficacy of estrogen supplementation in the treatment of urinary incontinence. The Continence Program for Women Research Group. Obstet Gynecol 1996;88:745-9.
18. FANTL JA, WYMAN JF, ANDERSON RL, MATT DW, BUMP RC. Postmenopausal urinary incontinence: comparison between non-estrogen-supplemented and estrogen-supplemented women. Obstet Gynecol 1988;71:823-8.
19. RUFFORD J, HEXTALL A, CARDOZO L, KHULLAR V. A double-blind placebo-controlled trial on the effects of 25 mg estradiol implants on the urge syndrome in postmenopausal women. International Urogynecology Journal 2003;14:78-83.

20. CARDOZO LD, WISE BG, BENNESS CJ. Vaginal oestradiol for the treatment of lower urinary tract symptoms in postmenopausal women--a double-blind placebo-controlled study. J Obstet Gynaecol 2001;21:383-5.
21. LOSE G, ENGLEV E. Oestradiol-releasing vaginal ring versus oestriol vaginal pessaries in the treatment of bothersome lower urinary tract symptoms. Bjog 2000;107:1029-34.
22. CARDOZO L, DRUTZ HP, BAYGANI SK, BUMP RC. Pharmacological treatment of women awaiting surgery for stress urinary incontinence. Obstetrics & Gynecology 2004;104:511-9.
23. ZULLO MA, PLOTTI F, CALCAGNO M, et al. Vaginal estrogen therapy and overactive bladder symptoms in postmenopausal patients after a tension-free vaginal tape procedure: a randomized clinical trial. Menopause 2005;12:421-7.
24. KINN AC, LINDSKOG M. Estrogens and phenylpropanolamine in combination for stress urinary incontinence in postmenopausal women. Urology 1988;32:273-80.
25. MATSUBARA S, OKADA H, SHIRAKAWA T, GOTOH A, KUNO T, KAMIDONO S. Estrogen levels influence beta-3-adrenoceptor-mediated relaxation of the female rat detrusor muscle. Urology 2002;59:621-5.
26. HERZOG AR, DIOKNO AC, BROWN MB, NORMOLLE DP, BROCK BM. Two-year incidence, remission, and change patterns of urinary incontinence in noninstitutionalized older adults. J Gerontol 1990;45:M67-74.
27. COYNE K, REVICKI D, HUNT T, et al. Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: the OAB-q. Qual Life Res 2002;11:563-74.
28. UEBERSAX JS, WYMAN JF, SHUMAKER SA, MCCLISH DK, FANTL JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. Neurourol Urodyn 1995;14:131-9.
29. SHUMAKER SA, WYMAN JF, UEBERSAX JS, MCCLISH D, FANTL JA. Health-related quality of life measures for women with urinary incontinence: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program in Women (CPW) Research Group. Qual Life Res 1994;3:291-306.
30. BURGIO K, GOODE P, RICHTER H, LOCHER J, ROTH D. Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: validation of three global patient ratings. Neurourol Urodyn submitted for publication.
31. COYNE KS, MATZA LS, THOMPSON CL. The responsiveness of the Overactive Bladder Questionnaire (OAB-q). Qual Life Res 2005;14:849-55.