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Ellington D[1], Malek J[1], Szychowski J[2], Kimberly G[3], Burgio K[4], Richter H[1]

1. *University of Alabama at Birmingham, Division of Urogynecology and Pelvic Reconstructive Surgery,* ***2.*** *University of Alabama at Birmingham, Division of Biostatistics,* ***3.*** *Park Nicollet Health, Urogynecology and Reconstructive Pelvic Surgery,* ***4.*** *University of Alabama at Birmingham, Department of Medicine, Birmingham/Atlanta Geriatric Research, Education, and Clinical Center, Department of Veterans Affairs*

LONGER-TERM OUTCOMES OF COMBINED TOLTERODINE AND VAGINAL ESTRADIOL CREAM FOR OVERACTIVE BLADDER SYMPTOMS AFTER SINGLE-THERAPY TREATMENT

Hypothesis / aims of study

The mainstays of treatment of women with overactive bladder (OAB) syndrome are pharmacotherapy and behavioral therapy [1]. In addition to anticholinergic therapy, the use of intravaginal estrogen to treat atrophy is often used as part of an overall pharmacologic treatment plan. The lower urinary tract shares a common embryologic origin with the lower genital tract and has been found to contain abundant estrogen receptors. Thus, an optimized estrogen milieu would be expected to have a beneficial effect on urinary tissue, symptoms, and function. We previously described the primary 3-month results of a randomized trial comparing single-therapy with extended-release tolterodine (Detrol LA®) vs. low-dose intra-vaginal estradiol (Estrace®) cream in the treatment of OAB symptoms in menopausal women [2]. The aim of this study was to characterize 6 and 12 month outcomes in women undergoing additional combined treatment.

Study design, materials and methods

This was a planned secondary analysis of a single-site randomized open-label trial in menopausal women with increased daytime urinary frequency, urgency, or nocturia symptoms, and/or urgency urinary incontinence. Originally, subjects were randomized 1:1 to receive either extended-release tolterodine, 4 mg taken orally on a daily basis, or intra-vaginal estradiol cream 0.5 grams nightly for 2 weeks, then twice weekly for the duration of the study. The primary outcome measure was the Overactive Bladder Questionnaire (OAB-q) bother score, and secondary outcome measures included the OAB-Q health related quality of life questionnaire (HRQL) total and sub-scale scores, Patient Global Impression of Improvement (PGI-I), and the Patient Satisfaction Questionnaire (PSQ). At 12 weeks, subjects were offered addition of the alternative therapy with follow-up at 6 and 12 months utilizing these same measures. Outcomes were assessed using independent sample t-tests. Within-group change in scores utilized paired t-tests and Wilcoxon signed-rank tests. Significance was defined as $p<0.05$.

Results

At 6 months, 28 out of 58 patients on combined therapy completed follow-up. There were significant within group change of OAB-q bother score from baseline to 6 months in both the tolterodine+estradiol cream ($p<0.0001$) and estradiol cream+tolterodine groups ($p=0.003$) (Table 1). Similar findings were noted for within group changes at 12 months (Table 2). However, no difference was noted in change between groups at 6 and 12 months (Tables 1 and 2).

Combined therapy outcomes at 6 and 12 months were compared to single therapy at 3 months (Figure). There was no significant within group change in the OAB-q bother score from 3 to 6 months in the tolterodine +estradiol cream group (-7.3±14.7, $p=0.10$); however, a significant improvement was noted in the estradiol cream+tolterodine group (-20.0±23.9, $p=0.008$), with no difference noted between groups ($p=0.11$). There were no significant changes noted in HRQL total or subscale scores in the tolterodine+estradiol group, except in the concern subscale ($p=0.04$); in the estradiol+tolterodine group, there were significant changes noted in the total and all subscales ($p\leq0.008$), except social ($p=0.16$). There were no significant between-group differences (all $p\geq0.11$) Similar findings were noted in the OAB-q bother score changes from 3 to 12 months with the tolterodine +estradiol cream group (-0.5±22.1, $p=0.94$) and the estradiol cream+tolterodine group (-16.7±23.3, $p=0.02$), with no difference between groups, $p=0.10$). There were no significant differences in the HRQL total or subscales within the tolterodine+estradiol cream group (all $p\geq0.15$); in the estradiol+tolterodine group, there was a significant change in HRQL total (13.3±23.0, $p=0.04$) and in the coping (18.2±28.6, $p=0.03$) and concern (17.7±24.3, $p=0.01$) subscales. There were no significant changes between groups (all $p\geq0.10$).

At 6 and 12 months (N=26), PSQ outcomes revealed that 88% and 84% of subjects, respectively, reported that they were “Completely” or “Somewhat Satisfied,” and 77% and 85% of subjects, respectively, reported that they were “Much Better” or “Better” on the PGI-I.

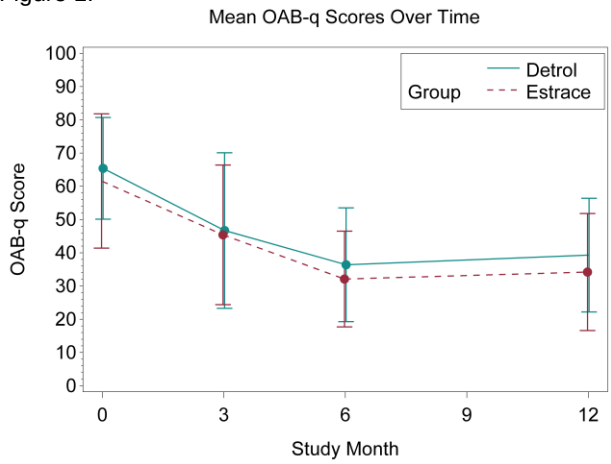
Table 1: Changes in Outcomes from Baseline to 6 Months

Outcome	Extended-release tolterodine (+estradiol cream) (n=14)	p (within group)	Estradiol cream (+tolterodine) (n=13)	p (within group)	p (for change between groups)
OAB-q	-25.4 ± 11.6	<0.0001	-28.7 ± 20.5	0.0003	0.61
HRQL total	19.3 ± 16.8	0.0009	20.9 ± 15.8	0.0005	0.80
Coping	22.1 ± 16.9	0.0003	23.3 ± 19.3	0.001	0.87
Concern	24.3 ± 22.0	0.0012	20.2 ± 18.5	0.002	0.61
Sleep	16.0 ± 21.5	0.02	27.1 ± 19.9	0.0004	0.18
Social	11.1 ± 20.3	0.06	12.0 ± 16.6	0.02	0.91

Table 2: Changes in Outcomes from Baseline to 12 Months

Outcome	Extended-release tolterodine (+estradiol cream) (n=11)	p (within group)	Estradiol cream (+tolterodine) (n=14)	p (within group)	p (for change between groups)
OAB-q	-23.4 ± 15.6	0.0006	-31.3 ± 24.3	0.0003	0.36
HRQL total	26.8 ± 20.5	0.002	19.7 ± 25.1	0.01	0.45
Coping	28.4 ± 19.1	0.0006	21.4 ± 27.2	0.01	0.48
Concern	31.4 ± 26.0	0.0025	19.8 ± 29.1	0.02	0.31
Sleep	22.5 ± 25.1	0.01	25.7 ± 25.9	0.003	0.76
Social	22.2 ± 19.4	0.004	10.6 ± 25.1	0.14	0.22

Figure 1.



Interpretation of results

Regardless of original assignment, subjects on combined therapy were significantly improved from baseline in both symptom bother and quality of life at 6 and 12 months. The treatment effect was sustained from 6 to 12 months. More improvement was noted from 3 months of single therapy to 6 and 12 months of combined therapy in the group originally assigned to intravaginal estradiol.

Concluding message

With the addition of the alternate therapy, OAB symptom severity and HRQL scores improved significantly at 6 and 12 months. On combined therapy, patients appeared to have an improved perception of symptom improvement as well as satisfaction. Larger and more robust long- term outcome studies are needed to better characterize the effects of combined medical therapy for OAB symptoms in menopausal women.

References

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Disclosures

Funding: Pfizer, Inc. awarded an Investigator Initiated Research Grant to conduct study
Detrol LA medication was provided by Pfizer, Inc.
Estrace Cream medication was provided by Warner Chilcott
Partially funded by the National Institutes of Diabetes and Digestive and Kidney Diseases 2K24-DK068389 – to Holly E. Richter, PhD, M.D. **Clinical Trial:** Yes **Registration Number:** Clinical Trials.gov NCT00465894 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** University of Alabama at Birmingham, Institutional Review Board for Human Use (IRB)
Protocol #X061208008 **Helsinki:** Yes **Informed Consent:** Yes