



## Female Urology – Incontinence

# Is There a Synergistic Effect of Topical Oestrogens When Administered with Antimuscarinics in the Treatment of Symptomatic Detrusor Overactivity?☆

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### Abstract

**Background:** No authors have investigated whether the administration of local oestrogens in addition to antimuscarinics could have a synergistic effect in the therapy of overactive bladder (OAB).

**Objectives:** To compare the efficacy of antimuscarinics alone versus antimuscarinics in combination with local oestrogens for OAB; to verify whether risk factors for lower antimuscarinic efficacy can be overcome by the concomitant use of local oestrogens.

**Design, setting, and participants:** Some 229 postmenopausal women with symptomatic urodynamically proven detrusor overactivity were prospectively enrolled at a tertiary level urogynaecology centre and divided into two groups.

**Intervention:** Women in group 1 ( $n = 129$ ) were prescribed tolterodine extended release (ER) 4 mg once daily; women in group 2 ( $n = 100$ ) were prescribed both tolterodine ER 4 mg and concomitant oestriol cream application once daily.

**Measurements:** All women underwent clinical evaluation and urodynamics in accordance with the Good Urodynamic Practices Guidelines. After 12 wk of treatment the two groups were compared in terms of subjective efficacy for OAB symptom improvement using a three-point scale. Nonresponders were compared to the patients who improved or were cured in order to identify risk factors for resistance to therapy.

**Results and limitations:** There was no significant difference between the two groups in terms of efficacy of therapy: 80.6% in group 1 versus 82% in group 2 ( $p = 0.86$ ). Patients with urodynamically proven detrusor overactivity (DO) occurring during provocative manoeuvres and patients with coital incontinence during orgasm reported a higher failure rate both in the overall study population and in group 2. A possible limitation of the study is the nonrandomised design.

**Conclusions:** No synergistic effect of local oestrogens and antimuscarinics in the treatment of OAB was found. Antimuscarinic treatment has lower cure rates in women with symptomatic DO complaining of incontinence at orgasm or in patients with DO following provocative manoeuvres. The association of local oestrogens does not influence the role of the two mentioned risk factors.

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## 1. Introduction

Overactive bladder (OAB) is a common condition characterised by urgency (with or without urge incontinence), usually with frequency and nocturia; its reported overall prevalence is about 12% in both men and women [1], and >50% of affected persons are deeply bothered by this syndrome [2]. The latest guidelines on the management of female urinary incontinence produced by the International Consultation on Incontinence (ICI) recommend, in the first instance, the evaluation of the women's hormonal status, suggesting oestrogen supplementation if needed [3]. However, the real efficacy of oestrogen therapy for the OAB is still controversial in terms of the type of oestrogen and the method of administration [4–6].

On the contrary, strong evidence is available on the efficacy of antimuscarinic treatment for OAB, particularly in the presence of a urodynamic diagnosis of detrusor overactivity (DO) [7–14]. Quite recently, Elinoff et al [15] reported the results of the IMPACT study that assessed the efficacy of 4 mg extended-release (ER) tolterodine (daily dose) in treating OAB in a primary-care setting. This study showed some of the best results ever published on this topic, reaching up to 78% in the reduction of urgency and 80% in urge incontinence, with only a small proportion of subjects who were not improved or cured after treatment. In the algorithm proposed by ICI, antimuscarinics are considered a second choice therapy, after oestrogen supplementation, pelvic floor exercises, and behavioural treatment [3]. Clinical and pharmacological research is currently trying to identify symptoms [16], risk factors [17], urodynamic criteria [18], and pathophysiological mechanisms [19] to predict which women with OAB would benefit from pharmacological therapy. Moreover, several authors are studying new molecules, new therapeutic strategies, and new methods of administration to improve the rate of treatment responders and the quality of life of women affected by symptomatic DO [20–22].

Despite the great number of reports regarding the efficacy of oestrogens or antimuscarinics on OAB symptoms, so far no author has tried to investigate whether the concomitant administration of these two drugs, acting on two different pathophysiological mechanisms, could have a synergic effect in reducing the rate of nonresponders to treatment.

The prospective study had two aims: (1) to compare the efficacy in OAB treatment of antimuscarinics alone versus antimuscarinics and concomitant local oestrogens and (2) to verify whether some factors previously reported to be associated

with a lower antimuscarinic efficacy can be overcome by the concomitant use of local oestrogens.

## 2. Methods

All postmenopausal women referred to the urogynaecology unit of King's College Hospital (London, UK) from January 2004 to September 2007 for symptoms of OAB and urodynamically proven pure DO (ie, without concomitant urodynamic stress incontinence) were included in this prospective study. We excluded women with documented recurrent urinary tract infections, previous antimuscarinic treatment, previous pelvic surgery, concomitant systemic hormone replacement therapy (HRT), history of breast cancer or endometrial cancer, neurological disease, clinical contraindications to treatment with oestrogen or antimuscarinics, and patients included in other ongoing clinical trials during the same study period.

Clinical evaluation included medical history, physical examination, a frequency–volume chart, and urinalysis. Pelvic-organ prolapse was assessed in the lithotomy position, with the patient exerting a maximal Valsalva maneuver, and was described according to the pelvic-organ prolapse quantification (POP-Q) system [23]. Women were considered to be postmenopausal if they were >40 yr old and reported absence of menses for at least 12 mo. All patients were studied with urodynamics using a standardised protocol in accordance with the Good Urodynamic Practices Guidelines of the International Continence Society [24]. Each patient was asked to attend urodynamic studies with a comfortably full bladder. Uroflowmetry was performed with the woman voiding in private and was recorded on a gravimetric flowmeter. Dual-channel cystometry was performed with the patient in the supine position; her bladder was filled through a 10F filling catheter and two fluid-filled 4.5F catheters were used to measure the intravesical (vesical catheter) and abdominal (rectal catheter) pressures. The bladder was filled with room-temperature saline at 100 ml/min. The filling catheter was removed when the patient developed a strong desire to void or when 500 ml had been infused into the bladder. Provocative manoeuvres were employed with the patient standing: She was asked to cough once, three times, and five times with maximal effort; to listen to running water; and to wash her hands in cold water. Finally each patient was seated for a pressure-flow study that was performed in private, and the post-void residual was measured using ultrasound scan imaging. All patients were examined by two trained urogynaecologists. All procedures and all definitions conformed to those of the International Continence Society [23,25]. We distinguished whether involuntary detrusor contraction occurred spontaneously during the filling phase or following provocative manoeuvres such as listening to running water or washing hands in cold water.

Patient evaluations and treatment prescriptions were performed by two trained urogynaecologists. Patients were divided into two groups: subjects in group 1 were prescribed only tolterodine ER 4 mg once daily to be taken at night for at least 12 wk; subjects in group 2 were prescribed both tolterodine ER 4 mg and concomitant oestriol cream application once daily to be taken at night for at least 12 wk. Patients

**Table 1 – Demographic characteristics of patients and distribution of risk factors for resistance to antimuscarinics**

Characteristic	Group 1 (tolterodine) (n = 129)	Group 2 (tolterodine + local oestrogens) (n = 100)	p value
Age (yr)	61 (42–85)	61 (40–81)	0.19 <sup>a</sup>
Parity	2 (0–5)	2 (0–9)	0.08 <sup>c</sup>
Body mass index	26.5 (20–41)	26 (19–37)	0.34 <sup>a</sup>
Delivery of a foetus >4000 g	32/129 (24.8%)	33/100 (33%)	0.19 <sup>b</sup>
Vacuum delivery	18/129 (14%)	19/100 (19%)	0.36 <sup>b</sup>
DO following provocative manoeuvres	24/129 (18.6%)	18/100 (18%)	1.00 <sup>b</sup>
Genital prolapse ≥2	30/129 (23.2%)	28/100 (28%)	0.23 <sup>b</sup>
Coital urinary incontinence at orgasm	4 (3.1%)	2(2%)	0.69 <sup>b</sup>

Abbreviation: DO, detrusor overactivity.  
<sup>a</sup> Student t test.  
<sup>b</sup> Fisher exact test.  
<sup>c</sup> Mann-Whitney U test.

were assigned to group 1 or group 2 in the following manner: Each of the two urogynaecologists always prescribed the same treatment to all patients; the assignment of the therapeutic regimen to each urogynaecologist was made randomly before the beginning of the study; the date of the visit was assigned by the booking centre of the King's College Hospital, which has no direct relation to the urogynaecology unit; both the patients in this study and the employees working at the booking centre did not know which of the two urogynaecologists was present the day of the visit.

The two study groups were evaluated after 12 wk of treatment and compared in terms of subjective efficacy for OAB symptoms improvement (urgency, frequency and urge incontinence): drug efficacy was assessed using a three-point symptom-assessment scale (0 = same, 1 = improved, 2 = cured) by a third independent investigator who was blinded to the therapeutic management assigned to each patient. Patients were defined as responders if they were improved or cured after 12 wk of therapy and as nonresponders if their urinary symptoms did not change with pharmacological therapy.

Nonresponders were compared to responders (ie, the patients who improved or were cured) in order to identify risk factors for resistance to drugs. Institutional Review Board approval and informed consent to participate in this study were obtained.

Statistical analysis was performed with GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, CA, USA) and Epistat 4.0 (Epistat Services, Richardson, TX, USA). Continuous variables were compared with Mann-Whitney U test or student t test as appropriate. Proportions of categorical variables were analysed for statistical significance using the Fisher exact test. Multivariable logistic regression analyses were used to assess the impact of risk factors for failure of therapy on the efficacy of antimuscarinics and oestrogens and to determine the interaction of covariates. A p value <0.05 was considered statistically significant.

The calculation of the power of the study considered the following data: a type I error of 0.05 and a power of 80%. Given an expected efficacy of 78% for tolterodine alone (data derived from the IMPACT trial [15]), a sample of 100 patients in the case group and 120 patients in the control group would have

allowed the demonstration of an improvement of 12% in the efficacy in the treatment group (tolterodine plus oestrogens).

### 3. Results

In this study we included 236 women with symptomatic, urodynamically proven DO. A total of 134 patients (56.8%) were assigned to group 1 and received tolterodine ER 4 mg daily for 12 wk, whereas 102 patients (43.2%) were included in group 2 and received vaginal oestriol for 12 wk in addition to tolterodine. Five patients in group 1 (3.7%) and two patients in group 2 (2%) did not take the treatment properly or were lost to follow-up; therefore, the final analysis included 129 patients in group 1 and 100 patients in group 2. The two groups were comparable in terms of demographic characteristics; the distribution of risk factors for resistance to antimuscarinics was similar in the two groups (Table 1). There was no significant difference in the rate of nonresponders to treatment: The efficacy of the therapy was 80.6% in group 1 and 82% in group 2 (p = 0.86), which is comparable to what is reported in the literature for antimuscarinics treatment alone (Table 2).

We then compared all nonresponders to those subjects who improved or were cured by the treatment. By univariate analysis, resistance to therapy was significantly higher in patients with urodynamically proven DO occurring during provocative manoeuvres and in those who had coital incontinence during orgasm among their overactive bladder symptoms (see Table 3). When we considered the group of patients treated with oestrogen in association with antimuscarinics (group 2), women with urodynamically proven DO on provocative manoeuvres had a significantly higher failure rate (8 nonresponders out of 18 patients [44.4%] had “provoked” DO versus 10 nonresponders out of the

**Table 2 – Efficacy of the two drug regimens in terms of cure, improvement, or rate of nonresponse**

Efficacy	Group 1 (tolterodine) (n = 129)	Group 2 (tolterodine plus local oestrogens) (n = 100)	p value	Odds ratio (95% CI)
Cured	81 (62.8%)	62 (62%)	1.00	1.03 (0.60–1.77)
Improved	23 (17.8%)	20 (20%)	0.73	0.87 (0.45–1.70)
Nonresponders	25 (19.4%)	18 (18%)	0.86	1.01 (0.56–2.14)

**Table 3 – Comparison of patients classified as responders and nonresponders**

Characteristic	Nonresponders (n = 43)	Responders (n = 186)	p value
Age (yr)	61 (40–81)	61 (42–85)	0.85 <sup>a</sup>
Parity	2 (0–5)	2 (0–9)	0.64 <sup>c</sup>
Body mass index	26.5 (21–34)	26 (19–41)	1.00 <sup>c</sup>
Delivery of a foetus >4000 g	12 (27.9%)	53(28.5%)	1.00 <sup>b</sup>
Vacuum delivery	8 (18.6%)	29 (15.6%)	0.64 <sup>b</sup>
DO following provocative manoeuvres	16 (37.2%)	26 (13.9%)	0.0009 <sup>b</sup>
Genital prolapse ≥2	10 (23.3%)	48 (25.8%)	0.84 <sup>b</sup>
Coital urinary incontinence at orgasm	4 (7%)	2 (1.6%)	0.01 <sup>b</sup>

Abbreviation: DO, detrusor overactivity.  
<sup>a</sup> Student t test.  
<sup>b</sup> Fisher exact test.  
<sup>c</sup> Mann-Whitney U test.

remaining 82 patients [12.2%];  $p = 0.0036$ ). Patients in group 2 who had coital incontinence during orgasm showed a significantly lower response to tolterodine compared to the others (2 nonresponders out of the 2 patients who mentioned the sexual symptom versus 16 nonresponders out of the remaining 98 patients [16.3%];  $p = 0.03$ ). Multivariate analysis confirmed that both DO occurring during provocative manoeuvres and coital urinary incontinence at orgasm are independent factors associated with a higher risk of failure of treatment in the general population of pharmacologically treated patients (DO during provocative manoeuvres: OR, 0.25; 95% CI, 0.11–0.52;  $p = 0.0002$ ; incontinence at orgasm: OR, 0.07; 95% CI, 0.01–0.42;  $p = 0.0035$ ). The association of tolterodine and local oestrogens did not modify the lower rate of responders in patients with DO occurring during provocative manoeuvres in multivariate analysis (OR, 0.13; CI 95%, 0.04–0.45;  $p = 0.0011$ ); the number of patients with incontinence at orgasm was too small to allow reliable multivariate analysis.

#### 4. Discussion

To the best of our knowledge, this is the first study reporting a comparison between antimuscarinics alone versus antimuscarinics in combination with local oestrogens for the treatment of OAB. Our data show no synergic effect of these two drugs on

symptoms of DO in postmenopausal women. This study also confirms that antimuscarinic treatment has lower cure rates in women with symptomatic DO complaining of incontinence at orgasm or in patients with a urodynamic diagnosis of DO following provocative manoeuvres. Moreover, the association of local oestrogens and standard antimuscarinic therapy does not have any influence on the role of the two mentioned risk factors in the group of nonresponders.

Administration of oestrogens has been extensively proven to be effective in the treatment of postmenopausal urogenital atrophy [6] and in the management of recurrent female urinary tract infections both in the fertile age (with oral contraception) [26] and after menopause [27].

On the contrary, despite being indicated by ICI as first-line treatment for postmenopausal women, the role of oestrogen supplementation in the treatment of urinary incontinence and OAB symptoms has not been clearly defined.

In 2003 a Cochrane meta-analysis on oestrogens and urinary incontinence considered 28 randomised or quasirandomised trials about this issue. The authors reported a significantly higher rate of subjective improvement or cure associated with the use of oestrogens versus placebo in patients affected by stress urinary incontinence, and even more in those with urge incontinence. On the contrary, the association of oestrogens with a progestogenic agent appeared to reduce the like-

likelihood of cure or improvement. The authors then stated that there were too few data to reliably address other aspects of oestrogen therapy such as oestrogen type, dose, and route of administration [4].

More recently, Hendrix et al [5] published a large randomised trial on >27 000 postmenopausal women who were given oral conjugated equine oestrogens with or without concomitant medroxyprogesterone acetate versus placebo in order to investigate the impact of systemic hormonal treatment on urinary symptoms. This study offered surprisingly strong evidence against the use of systemic oestrogens in the prevention or treatment of urinary incontinence: conjugated equine oestrogens increased the risk of developing de novo urge incontinence in women continent at baseline (risk ratio [RR], 1.32; 95% CI, 1.10–1.58), whereas in women complaining of urge urinary incontinence at baseline, symptoms of OAB got worse (RR, 1.47; 95% CI, 1.35–1.61).

Several other studies have failed to demonstrate any significant advantage of systemic oestrogen therapy for the treatment of urge incontinence [28–30]. These results do not seem to be affected by the route of oestrogen administration: in fact, even considering only those studies evaluating the effects of the use of local oestrogens, three different trials failed to prove any therapeutic effect on OAB symptoms [31–33]. In a recent review, Waetjen and Dwyer [34] concluded that the best evidence to date tells us that any oestrogen given by any route of administration should not be prescribed for the treatment of stress incontinence or urge incontinence in postmenopausal women.

In the controversy between international recommendations and level 1 evidence from well-designed studies, we have attempted to verify whether local oestrogens can at least improve the efficacy of concomitant antimuscarinic therapy in the group of women affected by symptomatic DO. Our findings confirm good efficacy for antimuscarinics (irrespectively of oestrogen supplementation), already demonstrated by us and other groups [12,15–18]. However, our findings show that restoring the vaginal oestrogenic pattern in postmenopausal women does not improve the efficacy of antimuscarinics in the treatment of OAB, and we therefore suggest that local oestrogen therapy should not be recommended in these cases. Moreover, the addition of oestrogen does not seem to modify the outcome of treatment in specific groups of patients affected by symptomatic DO with risk factors for lower efficacy of antimuscarinics. In particular, as also previously demonstrated, women with symp-

tomatic DO and urinary incontinence at orgasm do not frequently respond to antimuscarinic treatment, possibly because this form of DO has a different underlying pathophysiologic mechanism involving trigonal vanilloid receptors [35]. If this explanation could be confirmed, it could be logical that we did not observe any improvement with the addition of local oestrogens in these patients. Similarly, in women with urodynamic diagnosis of DO during provocative manoeuvres, a central neurogenic mechanism is more likely; they often fail to respond to antimuscarinics either alone or in combination to local oestrogens since these two drugs both have a prevalent peripheral action.

A limitation of the present study could be the absence of computerised randomisation. However, the assignment of each patient to one of the two schemes of treatment was not conditioned in any way but occurred randomly at the time of booking of the visit. The presence of a third investigator assessing drug efficacy and blinded to the group of treatment of the patients could have improved the objectivity of the results.

Another limitation of the present study is represented by the use of an asymmetrical three-item scale in the assessment of treatment efficacy of antimuscarinic therapy. However, Burgio et al [36] reported that a three-item scale has an “acceptable convergent and discriminant validity for measuring outcomes in studies of behavioural treatment for urinary incontinence” if compared to more complex questionnaires.

The design of this study did not allow for detection of improvements <12% in the local oestrogen group. However, it is possible that smaller differences, although statistically significant, might not be clinically relevant.

## 5. Conclusions

In this study, the administration of local oestrogen to postmenopausal women affected by urodynamically proven symptomatic DO did not demonstrate any synergic effect with antimuscarinics. Therefore, if these results are confirmed by further research, patients who are prescribed antimuscarinics treatment should receive oestrogens only if they are symptomatic for other urogenital problems such as vaginal atrophy and recurrent urinary tract infections. Postmenopausal women with DO occurring during provocative manoeuvres or with urinary incontinence at orgasm showed a lower response rate both to antimuscarinics alone and to antimuscarinics in combination with local oestrogens.

**Author contributions:** Maurizio Serati had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Serati, Salvatore.

**Acquisition of data:** Serati, Salvatore, Uccella.

**Analysis and interpretation of data:** Serati, Uccella.

**Drafting of the manuscript:** Serati, Salvatore, Uccella, Cardozo, Bolis.

**Critical revision of the manuscript for important intellectual content:** Serati, Salvatore, Uccella, Cardozo, Bolis.

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### Editorial Comment on: Is There a Synergistic Effect of Topical Oestrogens When Administered with Antimuscarinics in the Treatment of Symptomatic Detrusor Overactivity?

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In this issue, Serati et al [1] write about a study investigating the synergistic effect of topical oestrogens to tolterodine treatment, which failed to show the desired effects.

While the alpha error, the probability of showing a difference that does not really exist, in a trial is usually set to 5%, the beta error, the chance of missing out on an actual difference, is commonly 20% described as a power of 80%. That entails a 1:5 chance of missing out on an actual difference of clinical relevance. Thus, the fact that a study designed to show a difference fails to do so is by no means proof that no difference exists. To rightfully claim an absence of a difference, a study either has to be designed to show similarity or the power of the study has to be high enough that a failure to unearth a relevant difference is unlikely.

There was a time when negative trials were seldom published, but studies like Serati et al [1]

provide important information. They warn us that there might not be a benefit and that a new trial in this field should not only be sized for the difference we would like it to find but also powered so that a claim that no difference exists is reasonable in case of failure.

Increased power usually requires large trials. Thus, we will sometimes have to make do with a web of circumstantial evidence. If well-controlled trials repeatedly fail to show benefit for a therapy, we will eventually draw the conclusion that the likelihood of benefit is low. And while “innocent until proven guilty” is an excellent principle for the judicial system, “ineffective until proven effective” should be the principle for evidence-based medicine.

### Reference

- [1] Serati M, Salvatore S, Uccella S, et al. Is there a synergistic effect of topical oestrogens when administered with antimuscarinics in the treatment of symptomatic detrusor overactivity? *Eur Urol* 2009;55:713–20.

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### **Editorial Comment on: Is There a Synergistic Effect of Topical Oestrogens When Administered with Antimuscarinics in the Treatment of Symptomatic Detrusor Overactivity?**

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We know that in urinary stress incontinence, the symptoms of both stress and urge incontinence may coexist; however, this does not mean that detrusor overactivity (DO), a urodynamic diagnosis, may benefit from a combination of oral antimuscarinic and local oestrogens. Some postmenopausal women may benefit from local oestrogens for their symptoms of overactive bladder, but, based on our pathophysiologic knowledge, an improvement of detrusor overactivity is unlikely to be observed. Oestrogens have been used locally for the treatment of urinary stress incontinence; in fact, some results [1] suggest that oestrogen treatment alone, by an oral or vaginal route, could increase the blood flow around the bladder neck and midurethra and relieve the symptoms of overactive bladder and stress incontinence in postmenopausal women with prior hysterectomy. Vaginal preparations are as effective as systemic therapy at the lower serum level.

The changes of ageing are accelerated by a lack of oestrogen in hormonally dependent areas such as the vagina and the uroepithelium of the urethra. This change may result in incontinence due to irritative changes and in stress incontinence due to a loss of secretions, elasticity, and vascularity of

the urethra. Muscle weakness from atrophy, disuse, denervation, or oestrogen deficiency may also cause weakness of the intrinsic sphincter.

It is not surprising that the administration of local oestrogens to postmenopausal women affected by urodynamically proven symptomatic DO did not demonstrate any synergic effect with antimuscarinics. This corresponds to the findings of recent paper [2]. RCT reported conflicting evidence for the efficacy of oestrogens, even in treating stress incontinence in women. A meta-analysis showed that, when taken alone for a period of 3–6 mo, oestrogens have a higher cure and improvement rate compared to placebo [3], but insufficient data exist to determine the influence of the type of oestrogen, route of administration, and duration of therapy on treatment outcome.

### **References**

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