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Is Add-on Therapy with Vaginal Estrogen Better than Anti-Muscarinergic Therapy Alone in Treatment of Urgency Urinary Incontinence in Postmenopausal Women? - A Systematic Review and Meta-Analyses

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Review Article

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ABSTRACT

The purpose of this systematic review was to examine weather add-on therapy with vaginal estrogen exerts any benefits or side effects on urgency urinary incontinence in postmenopausal women. As part of a national guideline we aimed to systematically assess the existing literature on vaginal estrogen used in combination with Anti-muscarinic medicine in postmenopausal women with urgency urinary incontinence.

A systematic literature search was done in Medline, the Cochrane Library, EMBASE, CINAHL and PEDro from inception to June 2015. The primary search included guidelines and systematic reviews comparing vaginal estrogens as add-on to any Anti-muscarinic medicine compared to Anti-muscarinic medicine alone. The population was postmenopausal women with symptomatic overactive bladder syndrome with or without urgency urinary incontinence. In total 49 systematic reviews was identified and one was included. An updated literature search identified further 17 randomized controlled trials, but none was included. All studies were double-screened. In total 2 randomized controlled trials was eligible.

The evidence was of poor methodological quality. The study population was women with overactive bladder syndrome with or without urgency urinary incontinence. The pharmaceutical properties of the used vaginal estrogen differed from studies regarding specific estrogen type, dosage form and doses. There were no effects of add-on therapy with vaginal estrogen to Anti-muscarinic medicine regarding patient reported effect, urinary incontinence related quality of life, number of daily voidings, number of incontinence episodes daily. Furthermore the studies lacked reports on patient dropouts and harmful effects.

INTRODUCTION

Symptoms caused by vaginal mucosa atrophy following reduction or cessation of endogenic estrogen synthesis as a result of menopause are an established medical indication of vaginal estrogen therapy. In Denmark many postmenopausal women with urinary incontinence receive active treatment with vaginal estrogen regardless of having no symptoms of mucosa atrophy. The hormone treatment is often long-term and to many women results in certain costs. Therefore a working group as part of a National Danish guideline was established to assess whether or not treatment with vaginal estrogen has any beneficial or harmful effects on postmenopausal women with urgency urinary incontinence.

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MATERIAL AND METHODS

We performed a systematic literature search for existing systematic reviews and randomized controlled trials. We searched on Medline, the Cochrane Library, EMBASE, CINAHL and PEDro from inception to June 2015. The population was postmenopausal women with urgency urinary incontinence. The intervention was local vaginal estrogen therapy as add-on to Anti-muscarinic medicine compared to the Anti-muscarinic medicine alone. Minimum duration of treatment was three months. The pre-defined outcomes were patient reported effects measured by validated questionnaires such as UDI-6, urinary incontinence related quality of life measured by validated questionnaires such as IIQ-7, number of daily incontinence episodes, number of daily voidings, number of urinary tract infections, dropouts, serious adverse events, cancer and venous thromboembolic events. Timing of outcome reports was end of treatment and longest follow-up, minimum 6 months. We did not attempt to identify any unpublished literature.

The titles, abstracts, and full-texts when necessary were double-screened by two independent persons. When found eligible based on pre-determined criteria, two independent persons assessed articles. Two reviewers also did data extraction and assessment of methodological quality. Cochrane risk of bias tool from the Cochrane Handbook (http://handbook.cochrane.org/) and GRADE (www.gradeworkninggroup.org) was used. We followed the general principle of Cochrane Handbook Systematic Reviews of Interventions Manager and used the software RevMan to perform the meta-analysis. To each outcome an individual assessment of evidence was given. According to GRADE one of four levels of evidence was given: high quality of evidence, moderate quality of evidence, low quality of evidence and very low quality of evidence. The following domains were assessed in each included: risk of bias, inconsistency, indirectness, imprecision and publication bias. An overall guideline statement was then developed based on the beneficial and harmful effects of the intervention with respect to the quality of evidence of the outcomes in interest. According to GRADE the recommendations were either “strong” or “weak” based on the quality of the evidence and the used terms were either “recommend” or “suggest”.

RESULTS

The literature search identified several systematic reviews and randomized controlled trials. For details see flowcharts in **Figures 1 and 2.**

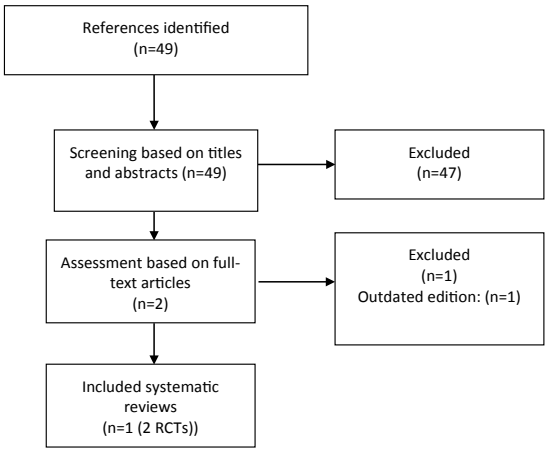

Figure 1. Literature search on systematic reviews.

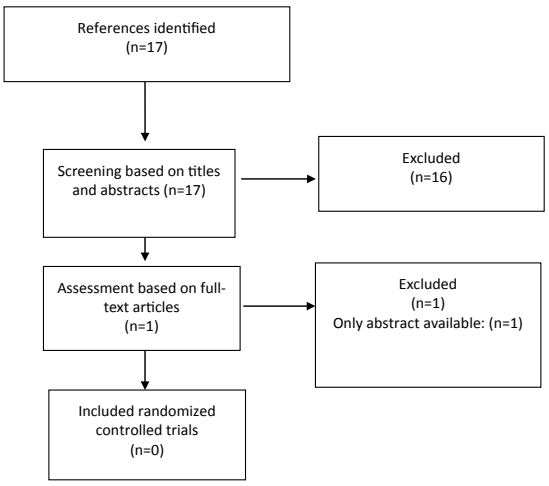

Figure 2. Literature search on randomized controlled trials.

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The included studies were randomized controlled trials [1,2]. The intervention was 12 weeks treatment with oral tolterodin 4 mg daily and 2 weekly application of vaginal estrogen crème with 0.625 mg conjugated equine estrogen (CEE) compared to oral tolterodin 4 mg daily alone [2]. Serati et al. did same intervention in their study, however the estrogen crème was applied daily but dosage form and dose was not specified [1]. The study population was postmenopausal women with symptomatic urgency/ overactive bladder syndrome, but not necessarily urgency urinary incontinence. All participants in the Serati study had urodynamic proven detrusor over activity, but in the Tseng study no urodynamic examination was done.

No effects were found on incontinence related quality of life, patient reported effects, number of episodes of incontinence, number of voiding's or dropouts. There was no evidence on serious adverse events, cancer, venous thromboembolic events and number of urinary tract infections **(Table 1).**

Table 1. Evidence profile.

Is add-on therapy with vaginal estrogen better than Anti-muscarinic therapy alone in treatment of urgency urinary incontinence in post-menopausal women?- A systematic review and meta-analyses							
Population: Postmenopausal women with urgency urinary incontinence Intervention: Vaginal estrogen treatment in minimum 3 months as add-on to Anti-muscarinic therapy Sammenligning: Oral treatment with Anti-muscarinic therapy in minimum 3 months							
Outcome (Timing)	**Absolute effect* (95% CI)**			**Relative effect 95% CI**	**Number of patients (studies)**	**Evidence level (GRADE)**	**Comments**
	Anti-muscarinic treatment	**Vaginal estrogen as add-on to Anti-muscarinic treatment**	**Difference with add-on with vaginal estrogen**				
Patient reported effect (End of treatment)	806 per 1000	749 per 1000 (435-1289)	57 fewer per 1000 (373 fewer-487 more)	RR 0.93 (0,54- 1,6)	229 (1) (1)	⊕⊕⊖⊖ LOW	Only 1 RCT with OAB population
Dropouts (End of treatment)					80 (1) (2)	⊕⊕⊕⊖ MODERATE	Only 1 RCT. No events in both groups
Cancer (Longest follow-up, min 6 months)						⊕⊖⊖⊖ VERY LOW	No evidence
Serious adverse events) (End of treatment)						⊕⊖⊖⊖ VERY LOW	No evidence
Venous thromboembolic event (End of treatment)						⊕⊖⊖⊖ VERY LOW	No evidence
Number of urinary tract infections (End of treatment)						⊕⊖⊖⊖ VERY LOW	No evidence
Patient reported effect (End of treatment)	mean 7.2	mean 6.9	MD 0.3 (1.53) fewer-0.93 more)		80 (1) (2)	⊕⊕⊖⊖ LOW	Only 1 RCT with OAB population. Used UDI-6 (range 0-100, the lower, the better
Number of voidings daily (End of treatment)	mean 6.4	mean 5.8	MD 0.6 (1.25 fewer-0.05 more)		80 (1) (2)	⊕⊕⊖⊖ LOW	Only 1 RCT with OAB population
Number of episodes of urgency incontinence daily (End of treatment)	mean 3.5	mean 3.3	MD 0.2 (0.44 fewer-0.04 more)		80 (1) (2)	⊕⊕⊖⊖ LOW	Only 1 RCT with OAB population
Incontinence related quality of life (End of treatment)	mean 6.5	mean 6.1	MD 0.4 (1.54 fewer-0.74 more)		80 (1) (2)	⊕⊕⊖⊖ LOW	Only 1 RCT with OAB population. Used IIQ-7 (range 0-100, the lower, the better)
*The basis for the control group absolute risks from the studies is mean risk across studies unless otherwise stated in comments. The intervention absolute risk and difference is based on the risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk Ratio; OR: Odds ratio, HR: Hazard ratio, MD: Mean difference, SMD: Standardized Mean Difference							
GRADE Working Group grades of evidence; High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.							

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DISCUSSION

Our findings support previous published systematic review by Rahn et al. [3]. Based on our findings we cannot recommend add-on therapy with vaginal estrogen as treatment of urgency urinary incontinence in postmenopausal women without any complaints of vaginal discomfort due to vaginal mucosa atrophy. There are no beneficial effects and information on side effects and long-term risks are sparse. Vaginal estrogen treatment is suggested as add-on therapy to other active treatment of urgency urinary incontinence when simultaneous complaints of symptoms of mucosa atrophy. Symptoms of mucosa atrophy in postmenopausal women are recurrent urinary tract infections, vaginal dryness, pain when urinating and burning sensation in urethra and introitus. When decision of treatment with vaginal estrogen is made several aspects must be considered. There are various pharmaceutical forms of vaginal estrogen which is dosed according to the Summary of Product Characteristics (SPC). Creams and pessaries applied twice weekly as maintenance dose and vaginal ring (hormone ring) applied deep into the vagina and worn continuously for three months and replaced with a new one. The woman's preferences must be exposed.

The included studies were of low methodological quality in several aspects. The included women were not all having urgency urinary incontinence, many of them having overactive bladder syndrome, but no incontinence. The intervention with estrogen crème applicated in the vagina is associated with risk of dose differences between participants and day-to-day variability. Further the doses were not reported in one of the included studies.

Our literature search showed that there is a need for further studies with randomized controlled trials with postmenopausal women with urgency urinary incontinence comparing vaginal estrogen treatment as add-on to Anti-muscarinic/beta3-agonist treatment to reveal any potential beneficial and/or harmful effects on urgency urinary incontinence.

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