Authors' objectives
To confirm that the use of estrogen therapy for urogenital atrophy is effective and to identify the efficacy of different estrogen dosage regimes, duration of therapy, and routes of administration.

Searching
Searches were made of MEDLINE, Excerpta Medica and BIOSIS Previews as well as handsearches of relevant journals published between January 1969 and April 1995. The search was restricted to original English language articles published in peer-reviewed journals.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) including placebo-controlled trials of parallel or cross-over design and uncontrolled trials were included if they fulfilled the following criteria: at least one of patient's symptoms, physicians report, changes in vaginal pH, and cytology change was reported; information was available on the study group treated with estrogen alone or in combination with a progesterone; sufficient information was provided to compare outcome measures between treated and control groups in RCTs or to estimate change from baseline in uncontrolled series. Series incorporating randomised comparisons between estrogen and other therapies but lacking a control group were classified as uncontrolled. Duration of study for placebo-controlled RCTs ranged from 3 to 34 weeks. Articles that did not contain at least one measurable outcome or were reviews, letters or abstracts were not included in the meta-analysis.

Specific interventions included in the review
Estrogen (given as various preparations and by various routes) and placebo were studied. Estrogen preparations included estradiol, conjugated estrogen, estriol and other (synthetic estrogen and combined preparations). Routes of administration included oral (various doses), vaginal (including tablets and cream), and parenteral (transdermal patches and sub-cutaneous implants).

Participants included in the review
Women with urogenital atrophy were studied. The age (presumably mean age) reported in a sub-group of placebo-controlled randomised trials ranged from 54.4 years to 72.1 years.

Outcomes assessed in the review
The following outcomes were assessed: patient's subjective report; dyspareunia; physicians report; changes in vaginal pH; vaginal cytology change; and serum estradiol and estrone levels.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
A standardised data collection sheet was used to collate data. No further details were given. In studies testing more than one drug and with each drug tested in a different group of patients, each treatment arm was used as a separate study.
studies using varying doses of drug, only the highest dose group was used. In studies using cross-over design, only one of the treatment groups (traditional oral preparation) was used.

**Methods of synthesis**

How were the studies combined?
The placebo-controlled RCTs were combined using the inverse normal method of Stouffer et al (see Other Publications of Related Interest).

An analogue of weighted analysis of variance was used to compare average effect size across all groups defined by the various protocols (type of estrogen, route of administration, and duration of therapy) and delivery systems. Pair-wise comparisons were considered if the significance was less than 0.05. Bonferroni correction was applied. When no baseline data were available, the control group data (if reported) was used as baseline measures.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**

Fifty-eight articles that included 10 placebo-controlled RCTs from 9 articles (N = 790) were included.

Few studies assessed treatment efficacy beyond 6 months.

P values for one-sided comparisons between active drug and placebo in RCTs: patient symptoms (6 trials) P < 0.001; dyspareunia (2 trials) P = 0.015; physician assessment (2 trials) P = 0.016; vaginal pH (2 trials) P = 0.001; cytology (5 trials): P < 0.001.

Effect of route of administration of estrogen: Some analysis based on very small number of studies. Vaginal route correlated with improvement in patient report, physician assessment, and significantly higher serum estrone levels. No difference was noted in dyspareunia between oral and parenteral. Parenteral administration led to higher estradiol and estrone levels. Type of estrogen: estradiol and estriol most effectively reduced patient symptoms; estriol most effectively reduced patient's dyspareunia; conjugated estrogen produced greatest increase in serum estradiol and estrone. Doses of estrogen with trials analysed in the following 4 groups: systematic taken as including all oral preparations apart from estriol, as well as transdermal patches, conjugated estrogen and subcutaneous implants; low dose oral estriol; low dose vaginal estriol; and low dose vaginal estradiol: low dose vaginal estradiol more effectively reduced patient's dyspareunia than systematic estrogen though was comparable to low dose oral estriol, systematic and low dose vaginal estradiol were equally effective in increasing serum estradiol and systematic estrogen most effective in increasing serum estrone.

Treatment duration: no consistent improvement in indicators of atrophy over time.

**Authors' conclusions**

Estrogen is efficacious in the treatment of vaginal atrophy and low-dose vaginal estradiol preparations are as effective as systematic estrogen therapy in the treatment of urogenital atrophy in post menopausal women.

**CRD commentary**

The aims of the review were clearly stated. The discussion includes mention of the following limitations of the review: studies were heterogeneous and lacked standardisation of patient selection, diagnostic criteria, study design, therapeutic intervention, and follow-up and outcome variables; probability of publication bias; and lack of assessment of patient compliance.

Details of keywords used for the literature search and mention of the journals considered relevant would have been helpful. Methods used to select primary studies and extract data were not described. Validity was not assessed. Inclusion criteria for participants and outcomes were not defined. Fuller details of the included RCTs would have been welcome.
By only reporting P value for the meta-analysis of RCTs, it was not possible to determine the clinical as opposed to statistical significance of the effect sizes calculated.

In view of the lack of definitions of participants and outcomes, and the lack of validity assessment the authors conclusions cannot be considered supported by the evidence presented.

**Implications of the review for practice and research**

Practice: The authors consider that the finding that low-dose local estrogen preparations are as effective as systematic estrogen in urogenital atrophy without the same increase in serum estrone or estradiol has important implications for clinical practice and research.

Research: The authors consider that further study is required into the use of low-dose local preparations for women who experience urogenital atrophy while receiving systematic hormone replacement therapy.

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**Other publications of related interest**


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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.