18th Expert Committee on the Selection and Use of Essential Medicines  
(21 to 25 March 2011)
Section 18: Hormones, other endocrine medicines and contraceptives
Section 18.4: Estrogens -- Ethinylestradiol (Possible deletion)

PROPOSAL FOR DELETION OF ETHINYLESTRADIOL AS A THERAPY FOR MENOPAUSAL SYMPTOMS AND OSTEOPOROSIS PROPHYLAXIS IN WOMEN FROM WHO MODEL LIST OF ESSENTIAL MEDICINES

Name of the organization preparing the application
School of Medicine, University of Split, Šoltanska 2, 21000 Split, Croatia
1. Stipic Ivica
2. Sambunjak Dario
3. Novak Ribicic Kristijana
4. Pehlic Marina
5. Strinic Tomislav

Acknowledgment
We thank Ana Utrobicic for her assistance in conducting literature search and obtaining the needed articles.

-------------

1. Ivica Stipic, MD, Resident doctor, Department of Obstetrics and Gynecology, University Hospital Split, Spinciceva 1, Split, School of Medicine, University of Split, Soltanska 2, 21000 Split

2. Sambunjak Dario, MD, PhD, Director, Croatian Branch of the Italian Cochrane Centre, Senior Editor of Croatian Medical Journal, School of Medicine, University of Split, Soltanska 2, 21000 Split

3. Novak Ribicic Kristijana, MD, Resident doctor, Department of Obstetrics and Gynecology, University Hospital Split, Spinciceva 1, 21000 Split

4. Pehlic Marina, MD, Research fellow, Department of Medical Biology, School of Medicine, University of Split, Soltanska 2, 21000 Split, CROATIA

5. Professor Tomislav Strinic, MD, PhD, Specialist in Obstetrics and Gynecology, Department of Obstetrics and Gynecology, University Hospital Split, Spinciceva 1, Split, School of Medicine, University of Split, Soltanska 2, 21000 Split
The aim of this review is to evaluate the efficacy of ethinylestradiol usage in peroral doses of 10 and 50 microgram for hormonal replacement therapy and osteoporosis treatment by searching all published papers and reports.

Ethinylestradiol is currently listed on the WHO Model List of Essential Medicines as a medicine used for contraception, hormonal replacement therapy and osteoporosis treatment.

**Introduction**

Estrogen, a steroid hormone, is derived from the androgenic precursors androstendione and testosterone by means of aromatization. In order of potency, naturally occurring estrogens are 17 (beta)-estradiol (E2), estrone (E1), and estriol (E3). The synthesis and actions of these estrogens are complex. Estradiol is primarily produced by theca and granulosa cells of the ovary, and it is the predominant form of estrogen found in premenopausal women. Estrone is formed from estradiol in a reversible reaction. This is the predominant form of circulating estrogen after menopause. Estrone is also a product of the peripheral conversion of androstendione secreted by the adrenal cortex. Estriol is the peripheral metabolite of both estradiol and estrone; it is not secreted by the ovary. Estrogens affect many systems, organs, and tissues, including the liver, bone, skin, gastrointestinal tract, breast, uterus, vasculature, and brain. These effects appear to become most prominent during times of estrogen deficiency, such as the menopausal transition[1].

The history of estrogen use began in the early 1900s, when ovarian extracts were popular for treating dysmenorrhea and amenorrhea[2]. Researchers isolated an ovarian extract that regularly caused estrus in animals in 1923 and evaluated the impact of ovarian extracts on menopausal symptoms in the late 1920s [3]. By 1928, the first commercially available injectable estrogen was developed[2]. In 1942, Ayerst Laboratories launched the first orally active estrogen, Premarin (conjugated estrogens), in the United States [4]. Since the 1940s, findings from a series of studies have had substantial effects on how estrogen therapy (ET) is used. Since their introduction in 1959, development of hormonal contraceptives has been ongoing, with the ultimate aim of creating not only an effective and safe contraceptive method, but also a drug able to meet the need for treatment of other conditions, such as acne, seborrhea, and hirsutism, with few or no side effects [5].

In the mid-1970s, researchers recognized the association between unopposed ET and endometrial cancer in women with an intact uterus [6]. These studies prompted the routine use of combination estrogen progestogen therapy (EPT) in women who had not undergone hysterectomy. In the following decades, some evidence also indicated that long-term ET/EPT use was associated with a small increase in the risk of breast cancer [7]. Accumulating evidence demonstrating the beneficial effects of ET/EPT on reducing the risk of osteoporotic fracture and coronary heart disease (CHD) suggested that these benefits outweighed the possible increase in the risk of breast cancer associated with ET/EPT [8].

Over the years, the number of prescriptions for hormone therapy has reflected scientific findings. In the 1970s, the number of prescriptions increased to approximately 30 million per year. This practice was likely due to data describing the cardioprotective effects of hormone therapy. In the 1980s, reports of increased rates of endometrial cancer with unopposed estrogen lead to a decrease in annual prescriptions to about 15 million. Then, the addition of progestogen for endometrial protection renewed interest in hormone therapy, and prescriptions again increased. Between 1995 and 2002, annual prescriptions peaked at about 91 million. Termination of the estrogen-progestin arm of the WHI in July 2002 and release of HERS II data received considerable media attention and raised serious questions about the safety of hormone therapy in postmenopausal women. Many women stopped taking hormones and began to seek out alternative therapies. Prescriptions for hormone
treatment immediately decreased. Of note, prescriptions for vaginal preparations did not change during this time [9].

Ethinylestradiol (EE), is a derivative of estradiol. Ethinylestradiol is an orally bio-active estrogen used in almost all modern formulations of combined oral contraceptive pills. The first orally active semi-synthetic steroidal estrogen, ethinylestradiol (17α-ethynylestradiol), the 17α-ethynyl analog of estradiol, was synthesized in 1938 by Hans Herloff Inhoffen and Walter Hohlweg at Schering AG in Berlin. It is one of the most commonly used medications. EE is released into the environment as a xenoestrogen from the urine and feces of people who take it as a medication. While estradiol is readily absorbed when taken orally, it is also quickly inactivated by the liver. Substitution at C17 of the estrane steroid with an ethinyl group proved to provide an estrogen that is much more resistant to degradation and paved the way for the development of oral contraceptives.

The most common use for ethinyl estradiol is in hormonal birth control, usually in the form of a combination medication which includes a form of progesterone or progestin. The use of ethinyl estradiol in birth control medications allows for low dosages, so that patients can receive the benefits without as many of the harmful side effects. Patients can receive the medication in oral form, or in the form of a patch, gel, or insertable medication which is delivered directly to the vagina [5].

Ethinylestradiol (EE) is the estrogen component of the majority of oral contraceptives marketed in the United States. Doses of EE for contraception range from 20 to 50 micrograms daily and are formulated with a progestin, commonly levonorgestrel or norethindrone. However, while EE is the nearly exclusive exogenous estrogen used by premenopausal women, at the time of the perimenopause or menopause, conjugated equine estrogens (CEEs) are used predominately to treat menopausal symptoms and prevent osteoporosis. Recently, lower doses of EE than those used in oral contraceptives have been administered continuously in combination with norethindrone acetate (NA) to postmenopausal women with an intact uterus as hormone replacement therapy (HRT) and have shown efficacy, in small numbers of patients, in reducing hot-flash frequency while maintaining an atrophic endometrium, increasing BMD, and not producing detrimental cardiovascular effects [10].

**Formulation and dosage regimens**

Several preparations are available for hormone therapy. They include estrogen therapy alone or estrogen in combination with a progestogen. Therefore, the addition of progestogen is advised for endometrial protection in women with a uterus. The exception is when low-dose estrogen is locally administered to treat vaginal atrophy. Preparations for estrogen or estrogen progestogen therapy include oral, transdermal, injectable and vaginal formulations. Transdermal delivery systems include patches, gels, sprays, and lotions, while vaginal products include suppositories, creams, and rings [11].

**Indications for use**

1) Contraception
2) Hormone replacement therapy (HRT)
3) Premature menopause
4) Prevention and treatment osteoporosis
5) Prevention of heart disease
6) Improves cognition
7) Delay Alzheimer's disease
8) Reduce the risk of colorectal cancer
9) Dysmenorrhea
10) Improve insulin resistance in patients with Type II diabetes
11) Vasomotor symptoms
12) Vaginal symptoms
13) Sexual function
14) Urinary health
15) Protective effect on osteoarthritis
16) Mood and sleep symptoms
17) Quality of life


Contraindications and Precautions

1) Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or a history of these conditions
2) Undiagnosed vaginal bleeding
3) Known sensitivity to the drug or any ingredients in the formulation
4) Markedly impaired liver function or liver disease
5) Carcinoma of breast
6) Active endometrial cancer
7) Gallbladder disease
8) Acute hepatic disease or damage
9) Conditions that might be aggravated by fluid retention (asthma, seizure disorders, migraine, cardiac or renal dysfunction)
10) Mental depression or a history of these conditions


Adverse effects

1) Fluid retention, edema, bloating, weight gain
2) Vaginal bleeding
3) Increased blood clotting
4) Nausea
5) Breast tenderness
6) Headache
7) Mental depression


Identification of clinical evidence – Literature Search and Strategy

Medline (Systematic Reviews and Randomized Controlled Trials), Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials were searched to identify all published papers and reports evaluating the evidence for and against the use of ethinylestradiol for menopausal symptoms and osteoporosis prophylaxis in women, compared to placebo and/or other medicines recommended for these indications (Figures 1-4).

Inclusion and Exclusion Criteria

Non-English language papers and studies of animals or cadavers were excluded.
Only 10 µg and 50 µg doses of ethinylestradiol were considered as well as studies with postmenopausal women only.
The studies in which ethinylestradiol was used as a part of combination of medicines were excluded from review.
Excluded were studies of women not undergoing the menopausal transition and experiencing menopause related symptoms, studies of aging and its effects, and biologically based studies that did not report epidemiological data relating to symptoms (e.g., studies of hormone levels). Only outcomes related to menopausal symptoms and osteoporosis were considered.
Titles and then abstracts of retrieved papers were reviewed. Studies were included for review if they were systematic reviews or randomized controlled trials (RCTs). Clinical trials which are not RCTs were also included if the data published in them was considered relevant for this review. The citation lists of included studies were searched to identify any additional studies.
From the literature obtained, data relevant for evaluation of ethinylestradiol effectiveness was extracted and tabulated.
Retrieved abstracts were entered into an electronic database (EndNote®).

Search strategies for Medline are shown below. The search strategies were adapted as necessary for each database.

Database: Ovid MEDLINE(R)
Search Strategy:

1. exp Ethinyl Estradiol/
2. (ethyl estradiol or oethinyl estradiol or ethinylestradiol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. Hot Flashes/
4. hot flash$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. Sweating/
6. ((night or nocturnal) adj5 sweat$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. exp Sleep Disorders/
8. (sleep$ adj5 disturb$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9. exp Vasomotor System/
10. vasomotor.mp.
11. exp Mood Disorders/
12. (mood adj5 change$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. mood swings.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. Depression/
15. depress$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
16. Anxiety/
17. anxi$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. exp Cognition/
19. (cogni$ adj5 function$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. exp Urinary Incontinence/
21. urinat$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
22 incontinen$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
23 exp Urogenital System/
24 (urogenital adj5 (atrophy or symptom$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
25 (vagina$ adj5 dry$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
26 Libido/
27 (loss adj3 libido).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
28 "Quality of Life"/
29 (quality adj5 (life or living)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
30 exp Menopause/
31 (menopaus$ or perimenopaus$ or postmenopaus$ or post-menopaus$ or postmenopaus$ or premenopaus$ or climacteric$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
32 1 or 2
33 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
34 (menopaus$ adj5 (symptom$ or sign$ or syndrome)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
35 33 or 34
36 30 or 31
37 32 and 35 and 36
38 randomized controlled trial.pt.
39 controlled clinical trial.pt.
40 randomized.ab.
41 placebo.ab.
42 drug therapy.fs.
43 randomly.ab.
44 trial.ab.
45 groups.ab.
46 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47 exp animals/ not humans.sh.
48 46 not 47
49 37 and 48

Database: Ovid MEDLINE(R)
Search Strategy:

1 exp Ethinyl Estradiol/ 9)
2 (ethinyl estradiol or oethinyl estradiol or ethinylestradiol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3 1 or 2
4 Osteoporosis, Postmenopausal/
5 osteoporo$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
6 Bone Density/
7 (bone adj3 (densit$ or loss or mass$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
8 BMD.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9 Fractures, Bone/
10 fracture$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11 4 or 5 or 6 or 7 or 8 or 9 or 10
12 3 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 random$.ab.
16 placebo.ab.
17 drug therapy.fs.
18 trial.ab.
19 groups.ab.
20 13 or 14 or 15 or 16 or 17 or 18 or 19
21 exp animals/ not humans.sh.
22 20 not 21
23 12 and 22
Records identified through Medline (n = 98)

Additional records identified through Cochrane Central Register of Controlled Trials (n = 46)

Records screened (n = 144)

The review of the titles and abstracts of these clinical trials did not indicate that they are evaluating the effectiveness of ethinylestradiol for menopausal symptoms

Records excluded (n = 118)

Articles eligible for further search (n = 26)

Records excluded (n = 18) because they did not refer to required doses, required hormone or menopausal symptoms

Studies included in tabular presentation of clinical trials (n = 2)
Figure 2. Flow diagram for identification of systematic reviews or meta-analysis evaluating the effectiveness of ethinylestradiol for menopausal symptoms

Records identified through Medline (n = 1)

Additional records identified through Cochrane Database of Systematic Reviews (n = 7)

Records screened (n = 8)

Records excluded (n = 6)
The review of the titles and abstracts of these systematic reviews showed that hormonal contraceptives, combination of medicines or other indications were investigated.

Full-text articles assessed for eligibility (n = 2)

Full-text articles were excluded (n = 2) because they did not refer to required doses of ethinylestradiol or menopausal symptoms.

Studies included in tabular presentation of clinical trials (n = 0)
Figure 3. Flow diagram for identification of clinical trials evaluating the effectiveness of ethinylestradiol for osteoporosis prophylaxis

Records identified through Medline (n = 141)

Additional records identified through Cochrane Central Register of Controlled Trials (n = 66)

Records screened (n = 207)

Records excluded (n = 183)
The review of the titles and abstracts of these clinical trials did not indicate that they are evaluating the effectiveness of ethinylestradiol for menopausal symptoms

Articles eligible for further search (n = 25)

Records excluded (n = 20) because they did not refer to required doses of ethinylestradiol or menopausal symptoms

Full-text articles assessed for eligibility (n = 5)

Records excluded (n = 3) Excluded article did not refer to required doses of ethinylestradiol, were not clinical trials or because of no extractable data

Studies included in tabular presentation of clinical trials after duplicates removed (n = 2)
After literature search and analysis of retrieved papers, 3 relevant clinical trials and 1 systematic review were identified evaluating the evidence for and against the use of ethinylestradiol for menopausal symptoms and osteoporosis prophylaxis in women (Table 1., Table 2. and Table 3.).

**Ethinylestradiol for the management of menopausal symptoms**

Retrieved clinical trials evaluating the effectiveness of ethinylestradiol for the management of menopausal symptoms are presented in Table 1.

### Table 1. Clinical trials evaluating the effectiveness of ethinylestradiol for the management of menopausal symptoms

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Study Type; Study Design</th>
<th>Findings; Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Speroff (1996) [10] placebo-controlled, double-blind, parallel-group, randomized clinical trial</td>
<td>Bone mineral density increased significantly from baseline (P&lt;.001) in the 1 mg NA-5 micrograms EE₂ and the 1 mg NA-10 micrograms EE₂ treatment groups at each annual assessment. Among the unopposed EE₂ groups, only the 10-micrograms group had increased BMD above baseline, but also was accompanied by an unacceptably high rate of endometrial hyperplasia. The NA-EE₂ treatment groups had a significant linear dose-response trend for increasing BMD. Increased endometrial proliferation and hyperplasia occurred with increasing unopposed estrogen doses. The combination of NA and EE₂ effectively protected the endometrium against hyperplasia. The percentage of change in the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol was positive for all treatment groups. The increase in triglyceride levels associated with EE₂ was attenuated with NA-EE₂ treatment. Daily treatment with NA-EE₂ was well tolerated and protected the endometrium from EE₂-induced proliferation and hyperplasia. The NA-EE₂ treatments produced a dose-related significant increase in BMD that was not present with unopposed EE₂ treatment. The overall effect of NA-EE₂ treatments on lipid measures was favorable.</td>
</tr>
<tr>
<td></td>
<td>Women aged 40 years or older who had undergone the onset of spontaneous menopause within the last 5 years (N = 1265)</td>
<td>Patients were equally randomized to placebo or 1 of 8 treatment groups: 0.2 mg of norethindrone acetate (NA) and 1 micrograms of ethinylestradiol (EE₂); 0.5 mg of NA and 2.5 micrograms of EE₂; 1 mg of NA and 5 micrograms of EE₂; 1 mg of NA and 10 micrograms of EE₂; 1 micrograms of EE₂; 2.5 micrograms of EE (₂); 5 micrograms of EE₂; or 10 micrograms of EE₂</td>
</tr>
<tr>
<td>02.</td>
<td>Dennerstein (1979) [12] Controlled clinical trial, double blind crossover trail</td>
<td>Ethinylestradiol was found to have a beneficial influence on aspects of affect such as Hamilton scores, anxiety irritability and insomnia. The influence of hormones on Hamilton scores could be partly but not fully explained by the alleviation of hot flushes. Norgestrel showed less favorable changes.</td>
</tr>
<tr>
<td></td>
<td>49 women who had previously undergone hysterectomy and bilateral oophorectomy</td>
<td>3 months each of ethinylestradiol-50</td>
</tr>
</tbody>
</table>


micron/day, levonorgestrel-250 micron/day, "Nordial"-a combination of these two substances, and placebo initially but these tended to diminish by the third therapy month
Most of the women studied were not clinically depressed. Anxiety symptoms were the major features exhibited in the group of women investigated

Summary of findings of clinical trials

All together 144 articles were reviewed. Only two relevant clinical trials published between 1988 and 1996 were identified. Only one of them[10] was deemed high quality. This study was a 2-year, double-blind, placebo-controlled, parallel-group clinical trial on 1265 postmenopausal outpatients with intact uterus at sixty-five centers. Patients were equally randomized to placebo or 1 of 8 treatment different groups. Subjects in the 10 micrograms ethinylestradiol group were terminated from the study early owing to a high rate of endometrial hyperplasia. Other groups with unopposed ethinylestradiol had minimal endometrium thicker than before starting therapy. The combination of norethindrone acetate (NA) and ethinylestradiol (EE2) effectively protected the endometrium against hyperplasia. Minimal impact on lipid and cholesterol metabolism is an additional reason that did not last application of ethinylestradiol as a estrogen replacement in postmenopausal women with intact uterus.

Second article is controlled clinical trial and double blind crossover trial [12]. The sample consisted of 49 women who had previously undergone hysterectomy and bilateral oophorectomy which condition is a prerequisite for therapy with EE2. Ethinylestradiol was found to have a beneficial influence on aspects of affect such as Hamilton scores, anxiety irritability and insomnia. Study investigated some minor menopausal symptoms.

Ethinylestradiol for osteoporosis prophylaxis

Retrieved clinical trials evaluating the effectiveness of ethinylestradiol for osteoporosis prophylaxis are presented in Table 2. Retrieved systematic reviews evaluating the effectiveness of ethinylestradiol for osteoporosis prophylaxis are presented in Table 3.

Table 2. Clinical trials evaluating the effectiveness of ethinylestradiol for osteoporosis prophylaxis

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Study Type; Study Design</th>
<th>Findings; Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Speroff (1996) [10] placebo-controlled, double-blind, parallel-group, randomized clinical trial</td>
<td>Bone mineral density increased significantly from baseline (P&lt;.001) in the 1 mg NA-5 micrograms EE2 and the 1 mg NA-10 micrograms EE2 treatment groups at each annual assessment. Among the unopposed EE2 groups, only the 10-micrograms group had increased BMD above baseline, but also was accompanied by an unacceptably high rate of endometrial hyperplasia. The NA-EE2 treatment groups had a significant linear dose-response trend for increasing BMD. Increased endometrial proliferation and hyperplasia occurred with increasing unopposed estrogen doses. The combination of NA and EE2 effectively protected the endometrium against hyperplasia. The percentage of change in the</td>
</tr>
</tbody>
</table>
or 10 micrograms of EE₂

ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol was positive for all treatment groups. The increase in triglyceride levels associated with EE₂ was attenuated with NA-EE₂ treatment.

Daily treatment with NA-EE₂ was well tolerated and protected the endometrium from EE₂-induced proliferation and hyperplasia. The NA-EE₂ treatments produced a dose-related significant increase in BMD that was not present with unopposed EE₂ treatment. The overall effect of NA-EE₂ treatments on lipid measures was favorable.

<table>
<thead>
<tr>
<th>02.</th>
<th>Horsman (1977) [13] prospective trial of postmenopausal women (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The effects on bone loss were compared for no treatment, treatment with estrogen, or treatment with calcium. The estrogen-treated group received ethinyl estradiol 25 or 50 mcg for 3 of every 4 weeks. Calcium-treated patients took 2 calcium gluconate tablets/day, equal to 800 mg of calcium.</td>
<td>Women treated with estrogen did not lose bone density. Those treated with calcium had some bone loss but less than the untreated subjects.</td>
</tr>
<tr>
<td>Women in the untreated control group continued to lose bone during the two years, whereas the estrogen-treated group lost none. Loss in the calcium-treated group was intermediate. Oestrogen appeared to inhibit endosteal bone resorption and may have stimulated subperiosteal bone apposition.</td>
<td></td>
</tr>
</tbody>
</table>

Summary of findings of clinical trials

Only two relevant studies of 207 articles reviewed regarding the effectiveness of ethinylestradiol for osteoporosis prophylaxis were identified. These studies are clinical trials published between 1977 and 1996. The first study [10] was a 2-year, double-blind, placebo-controlled, parallel-group clinical trial on 1265 postmenopausal outpatients with intact uterus at sixty-five centers. Patients were equally randomized to placebo or 1 of 8 treatment different groups. Bone mineral density (BMD) was measured by quantitative computed tomography. The NA-EE₂ treatment groups had a significant linear dose-response trend for increasing BMD. Among the unopposed ethinylestradiol groups, only the 10- micrograms group had increased BMD above baseline. Operated women participated in the second study[13]. The effects on bone loss were compared for no treatment, treatment with estrogen, or treatment with calcium. The estrogen-treated group received ethinyl estradiol 25 or 50 mcg for 3 of every 4 weeks. Women treated with estrogen did not lose bone density. Women in the untreated control group continued to lose bone during the two years. We can conclude that EE₂ treatment prevents postmenopausal bone loss.
Table 3. Systematic reviews evaluating the effectiveness of ethinylestradiol for osteoporosis prophylaxis

<table>
<thead>
<tr>
<th>No.</th>
<th>Article; Methodology</th>
<th>Remarks / Results concerning ethinylestradiol role</th>
<th>Conclusions; Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Doren (2003) [14] The objective of this study was to conduct a systematic review of 2-year trials, published between 1990 and December 2002, and assessing changes in BMD by any estrogen including ethinyl estradiol, any estrogen plus any progestin, or tibolone. Thirty-nine randomized, prospective, controlled 2-year trials were analyzed in pre-specified groups according to the profile of the compounds, assessing changes in BMD by any estrogen including ethinyl estradiol, any estrogen plus any progestin, or tibolone. Only one study (Speroff et al., 1996) evaluated the efficacy of EE at the dose of 10 mcg.</td>
<td>There is no apparent difference between the various oral and non-oral estrogen compounds given the pre-specified classifications. The mean effect size did not change if the largest single trial with a compound not generally recommended for prevention of post-menopausal bone loss (ethinyl estradiol) was excluded.</td>
<td>The finding that all estrogens, irrespective of the mode of administration, are effective in maintaining BMD agrees with major results of previous meta-analyses and structured reviews. In conclusion, all oral and non-oral, human and non-human estrogens appear to exert similar effects on BMD.</td>
</tr>
</tbody>
</table>

Summary of findings of systematic review

The objective of this study was to conduct a systematic review of 2-year trials, published between 1990 and 2002, and assess changes in BMD by any estrogen including ethinyl estradiol, any estrogen plus any progestin, or tibolone. 122 studies were retrieved, of which thirty-nine fulfilled the inclusion criteria. Of these, only one investigated the effect of ethinylestradiol on bone mineral density (BMD) (Speroff et al., 1996). Women with previous hysterectomy and/or bilateral oophorectomy participated in this study. There is no apparent difference between the various oral and non-oral estrogen compounds. The finding that all estrogens, irrespective of the mode of administration, are effective in maintaining BMD agrees with major results of previous meta-analyses and structured reviews. In conclusion, all oral and non-oral, human and non-human estrogens appear to exert similar effects on BMD.

Risk of bias assessment

Risk of bias was assessed for three included primary studies that provided meaningful and extractable data. The assessment was done by use of The Cochrane Collaboration's risk of bias tool, which addresses the following domains: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (Figs. 5 and 6). Information extracted from each report for the risk of bias tool is presented in the accompanying Excel spreadsheet, along with a judgment of low, high or unclear risk of bias, as described in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2 (updated September 2009). The Cochrane

Figure 5. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Green, yellow, and red color designates low, unclear, and high risk of bias, respectively. A cell was left empty if there was no self-reported outcome in the study.

Figure 6. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.
Summary of available safety data

After searching 358 references we concluded the following:
Hormone replacement therapy may be used to manage the menopausal symptoms, but it is currently recommended to be given at the lowest effective dose and regularly reviewed by women and their doctor. In case of women with an intact uterus, HRT comprising estrogen and progestogen to minimize the risk of endometrial hyperplasia which can develop into endometrial cancer. Estrogen alone is recommended only for women after hysterectomy. After searching all articles we identified 3 clinical trial studies and no systematic review or meta analysis with ethinylestradiol alone for treatment of menopausal symptoms. Also, after a literature search and analysis of retrieved papers, we found only 3 clinical trial studies and one review of ethinylestradiol alone as a medicine for osteoporosis prophylaxis. Although, WHO Model List of Essential Medicines in 2009 names ethinylestradiol as a representative estrogen, various medicines can serve as alternatives[15].
WHO recommended EE₂ as hormone replacement for menopausal symptoms (in combination with a progestogen, if necessary), osteoporosis prophylaxis, contraception in combination with a progestogen, but, it is not recommended as a first-line medicine for HRT and osteoporosis prophylaxis. Unfortunately, there were very few relevant studies, those that were identified were quite old. There is no new data to indicate that it should be considered for re-instatement.

Conclusion

Since its introduction in clinical practice and during the past decades, different estrogen derivatives were used for treating menopausal symptoms and preventing the bone loss associated with the menopause. Ethinylestradiol (EE) is a synthetic hormone which is primarily used in hormonal contraceptives, usually in the form of a combination medication which includes a form of progestin. In addition to preventing pregnancy, ethinylestradiol also reduces the risk of osteoporosis and breast cancer, and it can be used to regulate menstrual cycles. Previously, doses of ethinylestradiol for contraception range from 20 to 50 micrograms daily. But today, the dose of 50 mcg is too high and not used in oral contraceptives. Also, the dose of 10 micrograms ethinylestradiol has no practical application.

Given the small number of studies and references on the application of ethinylestradiol alone, we conclude that the use of ethinylestradiol alone has some limitations, such as it should only be administered only to women without uterus. In addition other estrogen derivatives are known to be more effective and more suitable. From 1996 until to today, no data has been identified supporting the use of ethinylestradiol alone. Our research has left us in a situation in this field with more questions than answers. Overall, we conclude that the WHO will not recommend ethinylestradiol alone as a first choice treatment of menopausal symptoms and osteoporosis prophylaxis from the list of essential medicines.
References:


