Is oestrogen therapy effective in the treatment of menopausal depression?

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SUMMARY. Fifty-five depressed menopausal patients took part in a randomized double-blind cross-over trial using 'Harmogen' (piperazine oestrone sulphate) and placebo. The Beck depression inventory, hot flush counts, and patients' subjective assessment of well-being were used to assess clinical status. Hormonal, biochemical and coagulation profiles were carried out. Hot flushes improved significantly on oestrogen compared with placebo. Depression scores and well-being showed significant and equal improvement on oestrogen and placebo. Significant improvement in flushes in patients on placebo was observed in the first half of the trial but did not occur in the second half, in patients who had previously taken oestrogen. No significant changes occurred in biochemistry. Coagulation tests showed acceleration of the prothrombin time in patients taking 'Harmogen' compared with those on placebo. Piperazine oestrone sulphate is a relatively weak but safe oestrogen preparation, effective in treatment of vasomotor symptoms but no more effective than placebo in the treatment of depression.

Introduction

DEPRESSION is a common disabling condition in general practice and is particularly prevalent at the menopause. Ballinger (1975) used the General Health Questionnaire (Goldberg, 1972) to screen 760 middle-aged female patients on general practitioners' lists in Dundee and found that neurotic complaints and depression reached a peak incidence in the two years before the menopause. Kerr (1976) claimed that conjugated equine oestrogens were effective in the treatment of depressed menopausal patients although large doses were sometimes necessary to maintain satisfactory improvement. In 1976 Aylward (1976) reported a placebo-controlled trial of piperazine oestrone sulphate for one month in the treatment of depressed menopausal women and, using the Hamilton rating scale, found a significant improvement in oestrogen treated patients compared with those on placebo.

Aim

It seemed desirable to confirm these reports by a randomized controlled trial carried out over a longer period and including tests of blood coagulation, biochemistry and hormone profiles. In carrying out this trial the severity of depressive illness was examined in patients around the menopause and correlations were sought between this and hot flushes or hormone profile. The response of depressive illness to oestrogen therapy was measured and compared with the response to matching placebo tablets. Compliance was measured by serum oestrone levels. Effectiveness of the oestrogen preparation used was estimated by the reduction in patients' hot flush counts, compared with that obtained in a previous similar controlled trial by the same author using a different standard oestrogen preparation (Coope et al., 1975).

Methods

The patients

The patients were all on the NHS list of a semi-rural group practice of 7,500 between 1976 and 1978. A notice in the surgery waiting room asked women who were aged 40 to 60 and suffering from flushes or depression to see the doctor. When they attended, I enquired about contra-indications to oestrogen therapy such as breast or genital cancer, thrombo-embolism or thyroid, hepatic or renal disease; if there was no contra-indication, patients were accepted for inclusion in the trial. Those who had previously taken any type of hormone preparation ceased therapy for six months before starting treatment. They were informed that they would be receiving oestrogen but that their treatment would be inactive for part of the time; the design of the trial was not disclosed. Ethical approval was obtained.
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from the Research Committee of the Royal College of General Practitioners.

Trial design

Patients were given a code number and were allotted at random to one of two groups. Group 1 (29 patients) received piperazine oestrone sulphate 1.5 mg b.d., 21 days out of 28 for six months, followed by non-matching placebo tablets for two months, then placebo tablets which matched the oestrogen, twice daily 21 days out of 28 for six months. Group 2 (26 patients) received the treatments in reverse order. Treatment given in the first and last six months was double-blind. Neither the patients, their doctor nor the laboratory staff knew whether the patient was taking oestrogen tablets or matching placebo. Treatment given during the seventh and eighth months was single-blind. Thus there was a two months' gap between the two halves of the trial, which allowed withdrawal flushes to settle in patients taking oestrogen for the first six months. (In our previous controlled study of equine conjugated oestrogens (Coope et al., 1975) we found that the appearance of flushes in patients withdrawn from oestrogen therapy warned them that they were taking placebo tablets and so revealed the design of the trial.)

The doctor recorded the patient's age, date of last menstrual period, hysterectomy or oophorectomy, previous medical history and their smoking and social history. Symptoms were recorded, particularly vaginal dryness. Patients were shown how to complete the short form of the Beck depression inventory (Beck et al., 1961) and the score was assessed by the doctor. The patients were also asked to assess their present health as a percentage of what they expected to feel like when they were well, e.g. 60 per cent. They completed a diary card for each month, recording the number of hot flushes and sweats experienced during each period of 24 hours. Patients were examined before and after treatment; pelvis and cardiovascular system, including blood pressure and leg veins were checked. Urine was tested for albumin and sugar. They were referred for endometrial biopsy if they had suffered from intermenstrual bleeding or post-menopausal bleeding and all were biopsied within a year of starting therapy.

Severely depressed or suicidal patients were referred to a psychiatrist or admitted to hospital and did not take part in the trial.

Laboratory tests

Full blood count was arranged. Fasting blood was collected and centrifuged and half the sample was used for biochemical profile: calcium, phosphate, glucose, urea, uric acid, cholesterol, total protein, albumin, globulin, bilirubin, alkaline phosphatase, aspartate amino-transaminase, pregnancy-associated globulin and triglycerides. The other half was used for estimation of FSH, LH, prolactin, oestradiol and oestrone levels. The first 33 patients enrolled also had detailed tests of blood coagulation, as described elsewhere. (Coope et al., 1975; Poller et al., 1980).

Supervision

Patients were seen every two months, when their diary cards were exchanged for new ones, symptoms or side-effects were discussed and a fresh supply of tablets issued. At six months, eight months and 14 months they again completed the Beck inventory, assessed their state of well-being and had fasting blood tests of hormonal levels, biochemistry and blood coagulation.

Statistical methods

The Wilcoxon matched-pairs signed-ranks test was used to compare base-line values in individual patients with those occurring at different stages of treatment. The unpaired t-test was used to compare group mean clinical scores and oestrone and FSH levels at each stage in the two groups. A correlation was sought between base-line flush counts, Beck depression scores and serum oestrone, FSH levels and pregnancy-associated globulin.

Results

Fifty-five patients completed the trial. Two died, one of recurrence of gastric carcinoma, one after epileptic seizures following withdrawal of barbiturate therapy. These were not included in the analysis. There was no evidence of thrombo-embolic disease in either case. The following side-effects were attributed to therapy with piperazine oestrone sulphate: severe breast swelling (one case); fluid retention and left ventricular failure with gallop rhythm, basal crepitations and sacral oedema which resolved on withdrawing oestrogen and treatment with frusemide (one case); two patients developed severe depression after three months on oestrogen therapy and were admitted to hospital. No patient on matching placebo deteriorated sufficiently to be admitted to hospital. Although randomized, the groups appeared to be comparable with regard to age, hysterectomy status, flush accounts, depression scores and hormone levels at the beginning of the trial (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of patients.</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>48.3</td>
<td>48.2</td>
</tr>
<tr>
<td>Hysterectomy and oophorectomy</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Hysterectomy: ovaries conserved</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Natural menopause</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Still menstruating</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Flush: weekly group mean</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Depression scores: group mean</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Well-being assessment: percentage</td>
<td>52</td>
<td>51</td>
</tr>
<tr>
<td>FSH (U/L) group mean</td>
<td>43</td>
<td>47</td>
</tr>
<tr>
<td>Serum oestrone (pmol/l): group mean</td>
<td>279</td>
<td>282</td>
</tr>
</tbody>
</table>

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Depression scores
Both groups were comparable for depression scores at the start of the trial; mean scores were 15 and 16 respectively. Most patients scored over 10, falling into the category of 'cases' of depression; seven patients in each group scored 20 or over, falling into the category of 'moderately severe' depression. Two extremely depressed patients with scores of over 30 were not accepted for the trial but referred immediately to a psychiatric hospital. Two further patients were admitted to hospital during the trial because of depressive illness: both had taken oestrogen for three months at the time of admission.

Both the trial groups improved significantly and equally during each trial period of six months, irrespective of therapy (Figure 1).

There was no evidence to suggest that depression scores improved more in patients taking piperazine oestrone sulphate than in those taking placebo, or that patients' psychiatric state deteriorated when oestrogen was withdrawn and replaced with placebo.

The total number of consultations made by the study group during the periods they were on oestrogen was 287. The total number during the placebo periods was 277. Prescriptions for psychoactive drugs were kept to a minimum during the trial and are shown in Table 2.

There was no difference between the groups in the number of consultations or the number of prescriptions for psychoactive drugs.

Hot flushes
At the start of the trial the two groups were comparable in mean flush counts per week, which were 33 and 28. For the first two months both groups showed significant and equal improvement in flushes due to a high placebo response (Figure 2). After two months the groups diverged. Patients taking placebo showed no further improvement but did not deteriorate. Patients taking oestrogen continued to improve up to five months, when their group mean count was significantly lower than that of the placebo group (p<0.05). From the sixth to the eighth month, patients who were withdrawn from oestrogen and given placebo deteriorated sharply, returning rapidly to base-line levels of flushes. They did not improve on matching placebo tablets during months eight to 14.

Patients changing from placebo to oestrogen in the second half of the trial showed significant improvement over base-line counts from month nine to 14 (p<0.01). Thus, ‘Harmogen’ (piperazine oestrone sulphate) was significantly better than placebo in reducing hot flushes.

A significant placebo effect occurred during the first two months but was not observed during the second half of the trial in patients who had previously taken oestrogen.

Assessment of well-being showed that both groups of patients improved significantly and equally in both halves of the trial, irrespective of therapy.

Hormone profiles
Serum oestrone levels rose significantly and FSH levels fell correspondingly in patients taking oestrogen (Figure 3). No correlation was found between symptoms and hormone levels.

Biochemistry
No significant changes occurred in any of the parameters.

Coagulation
The prothrombin time was significantly accelerated in Group 1 patients after six months’ treatment with ‘Harmogen’, but changes in coagulation were less marked than those which have been reported in patients taking conjugated equine oestrogens (Coope et al,

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Table 2. Prescriptions for psychotropic drugs.

<table>
<thead>
<tr>
<th>Patients on oestrogen</th>
<th>Patients on placebo</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25 mg</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>25 mg</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>50 mg</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>25 mg</td>
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<tr>
<td>Phenobarbitone</td>
<td>30 mg</td>
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</table>

<table>
<thead>
<tr>
<th>Patients on placebo</th>
<th>25 mg</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>25 mg</td>
<td>6 months</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg</td>
<td>6 days</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>5 mg</td>
<td>6 days</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>30 mg</td>
<td>6 months</td>
</tr>
</tbody>
</table>

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Figure 2. Hot flushes. Mean values for the two groups.

Figure 3. Serum oestrone. Mean values for the two groups.

1975). A full account of the coagulation tests and results is published elsewhere (Poller et al., 1980).

Discussion

Depression is a common clinical problem in menopausal patients (Ballinger, 1975). It is so disabling both for the patient and her family that it is important for general practitioners to be able to make an accurate diagnosis and to treat it effectively. The success of oestrogen replacement in the treatment of the flushing and depression which often follows oophorectomy in younger women (Jacobs and Murray, 1976) should prompt the general practitioner to examine very carefully the possibility that oestrogen therapy may be useful in the management of depression in older menopausal patients. This study was designed to do this as objectively as possible.

First, the entry of patients to the treatment groups was randomized. However, although randomized, the two groups at entry had very similar age ranges and symptom severity, implying that the samples were large enough to be equally representative of the study population. The patients complied with the treatment schedule: this was demonstrated by the highly significant rise in serum oestrone levels in the patients on active tablets and the low levels in the patients taking placebo. The method which was used to assess the severity of depression and its response to treatment—the Beck depression inventory (Beck et al., 1961; Beck, 1967)—has been criticized by Campbell (1975) as being too insensitive to detect the fine changes which occur in menopausal patients. However, Campbell's criticism was made at the end of a double-blind trial in which the Beck inventory showed a highly significant improvement in his patients taking oestrogen and also those taking placebo. This does not necessarily imply a method failure but merely that there was in fact a high placebo response in his depressed menopausal patients. These findings are similar to our own, and also to those of Utian (1972), who concluded after a single-blind trial of oestrogen therapy in menopausal women that only flushes, sweats and atrophic vaginitis responded better to oestrogen than to placebo. Utian concluded that oestrogen was no more effective than placebo in the treatment of depression, irritability, dyspareunia, lack of libido and headache.

The Beck inventory has been thoroughly validated by Beck, who found a high correlation between depression scores and the clinical judgement of a team of experienced psychiatrists. Johnson and Heather (1974) examined the sensitivity of the inventory to changes in depressive symptoms in general practice and found that a change in clinical ratings was always accompanied by an appropriate change in the Beck score. However, he found that the Beck score was more sensitive than the clinical ratings and could be used to predict changes in them.

The evidence of this present trial, that oestrogen therapy with 'Harmogen' was not effective treatment for depression at the menopause, should therefore be accepted as valid.

Was this particular oestrogen preparation effective in treating menopausal symptoms? The response of flushes showed that after six months the group treated with oestrogen had significantly lower flush counts than those treated with placebo. Thus 'Harmogen' was effective in treating menopausal flushing. It has been claimed that 'Harmogen' is the preferred preparation at the menopause on grounds of safety (Journal of the Royal College of General Practitioners, 1977). The present study does not support such a view. Acceleration of extrinsic clotting occurred after six months' treatment with 'Harmogen' (Poller et al., 1980). The
change was less marked and slower to occur than the coagulation changes observed in patients treated with 'Premarin' (conjugated equine oestrogens) (Coope et al., 1975). However, it must be shown that the differences in side-effects are not merely an expression of a less potent preparation. Hart (1978) has shown that coagulation changes in patients treated with oestriol hemisuccinate increase in proportion to the dose of oestrogen used.

A significant improvement in flushes occurred in our patients who took placebo tablets before the cross-over but was not observed during the second half of the trial. This phenomenon was observed during our earlier study (Coope et al., 1975). It implies that the administration of exogenous oestrogen inhibits the subsequent spontaneous remission of flushes which often occurs in untreated patients. Perhaps this accounts for the phenomenon of so-called 'oestrogen dependence'—patients are reluctant to stop taking oestrogen as they experience severe flushing on withdrawal, and feel that this is an indication for continued therapy.

Perhaps it would be appropriate to discuss briefly the ethics of this trial. 'Unopposed' oestrogen therapy is now regarded as being associated with an increased risk of endometrial cancer (Smith et al., 1973; Weiss et al., 1976; Antunes et al., 1979), and most workers now accept the need for progestogen supplements in long-term therapy (Thom et al., 1979; Whitehead et al., 1977). However, at the time of the trial (1976 to 1977) the validity of the American reports was questioned by Studd and others (Studd, 1976) and the simplicity of an 'unopposed' oestrogen regime was regarded as more appropriate to a trial of treatment for depression. Readers who prescribe combined oestrogen-progestogen therapy will be familiar with the 'pre-menstrual' depression which may occur in patients taking a combined preparation. The ethics of any trial of a treatment for depression have to be carefully weighed. Very severely depressed or suicidal patients were not accepted for inclusion in this study but were referred immediately to a psychiatrist; worsening of symptoms to a dangerous level during the trial resulted in immediate referral or admission. The patients were carefully assessed at entry and re-assessed every two months; as the work was carried out by the patients' general practitioner any deterioration was immediately apparent and appropriate action was taken. In fact two patients were lost to the trial in this way.

**Conclusion**

The conclusions of the present study, which was carried out in general practice by the patients' own family doctor, are that oestrogen therapy is no more effective than placebo in the treatment of menopausal depression in middle age, and that there is insufficient evidence to support the view that 'Harmogen' is the preferred preparation at the menopause.

**References**


Acknowledgements

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