Hormonal replacement therapy does not affect self-estimated pain or experimental pain responses in post-menopausal women suffering from fibromyalgia: a double-blind, randomized, placebo-controlled trial

Kent D. Stening1,2, Olle Eriksson3, Karl G. Henriksson4, Jan Brynhildsen5, Lotta Lindh-A˚strand5, Göran Berg5, Mats Hammar5, Åsa Amandusson6 and Anders Blomqvist1

Abstract

Objectives. FM is a condition that preferentially affects women. Sex hormones, and in particular oestrogens, have been shown to affect pain processing and pain sensitivity, and oestrogen deficit has been considered a potentially promoting factor for FM. However, the effects of oestrogen treatment in patients suffering from FM have not been studied. Here, we examined the effect of transdermal oestrogen substitution treatment on experimental as well as self-estimated pain in women suffering from FM.

Methods. Twenty-nine post-menopausal women were randomized to either 8 weeks of treatment with transdermal 17β-oestradiol (50 μg/day) or placebo according to a double-blind protocol. A self-estimation of pain, a set of quantitative sensory tests measuring thresholds to temperature, thermal pain, cold pain and pressure pain, and a cold pressor test were performed on three occasions: before treatment, after 8 weeks of treatment and 20 weeks after cessation of treatment.

Results. Hormonal replacement treatment significantly increased serum oestradiol levels as expected (P < 0.01). However, no differences in self-estimated pain were seen between treatment and placebo groups, nor were there any differences between the two groups regarding the results of the quantitative sensory tests or the cold pressor test at any of the examined time points.

Conclusion. Eight weeks of transdermal oestradiol treatment does not influence perceived pain, pain thresholds or pain tolerance as compared with placebo treatment in post-menopausal women suffering from FM.

Trial registration. ClinicalTrials.gov Registration; http://www.clinicaltrials.gov; NCT01087593.

Key words: Oestrogen, Substitution, Pain, Hormonal levels, Quantitative sensory testing, Cold pressor test.

Introduction

FM is a clinical syndrome associated with widespread pain and the presence of specific tender points, as further defined by the ACR [1]. The syndrome is associated with sleep disturbances, mood disorders, fatigue and anxiety. Even though a multitude of studies have indicated pathological changes in the peripheral nervous system as well as the CNS in association with FM [2, 3], its aetiology remains unclear and the patient group is heterogeneous [4].
The multifactorial pathogenesis, the suffering and low quality of life in this group of patients, the lack of spontaneous recovery and the subsequent large costs for the health-care system [5] have led to a continuous search for new therapeutic options. Recently, several randomized, double-blind studies have been able to show significant effects of some of the drugs commonly used in FM treatment such as different antidepressants [6, 7]. Still, many drugs commonly used to treat patients with FM have not been evaluated. Among these drugs are oestrogens. There is, however, some experimental support for using oestrogens or other similar HRT regimens in FM. Several experimental studies in animals and human subjects have shown that oestrogens may affect pain processing and pain sensitivity, even though the results remain variable and somewhat inconsistent [8, 9]. Oestrogen-responsive cells in the superficial dorsal horn of the spinal cord produce pain-inhibiting substances such as endogenous opioids [10] and oestradiol may induce an increase in the spinal cord expression of these endogenous opioids [11, 12], suggesting a possible pain-modulatory role of oestrogens in these areas [13]. There is also a gender difference in pain sensitivity [14] as well as in the risk of acquiring certain pain conditions [15]. This is particularly evident for FM, which is far more common among women than among men [16]. Furthermore, the incidence of FM peaks in mid-life when the menopause transition occurs, and the symptoms in women suffering from chronic pain vary in intensity along with hormonal changes [17]. Oestrogen deficiency has thus been considered a potentially promoting factor for FM [18], and FM-like symptoms have been reported after oestrogen levels have been reduced following treatment with gonadotropin-releasing hormone analogues [19], as well as after rapid withdrawal of HRT [20, 21]. HRT has been associated with the alleviation of muscular pain in some studies [22, 23] and in a recent study of hormonal treatment in transsexual individuals, the administration of oestrogens/anti-androgens or androgens did induce changes in the prevalence of chronic pain [24]. Taken together, several studies do theoretically support the use of oestrogens in the treatment of FM. Such treatment has indeed been recommended [18, 25] and, according to many web forums and online medical consulting pages, this treatment is still widely used [pages obtained by searching (FM oestrogen treatment) in Google]. Thus, even though the clinical effect of oestrogen treatment has not been validated, oestrogen use remains a commonly recommended treatment option. Long-term HRT has potentially hazardous side effects, however, with an increased risk of breast cancer and cardiovascular events [26], and therefore HRT should be used with caution.

The objective of the present study was to fill the gap of knowledge on the effect of oestrogen substitution on pain in FM. For this purpose, post-menopausal women who had been diagnosed with FM were given treatment with transdermal 17β-oestradiol or placebo according to a double-blind protocol. Pain perception and pain threshold were determined using a set of quantitative sensory tests, and ongoing pain was rated by the participants using a pain map. The results show that oestrogen substitution does not influence perceived pain, pain thresholds or pain tolerance as compared with placebo treatment in post-menopausal women suffering from FM.

**Materials and methods**

**Participants** Twenty-nine post-menopausal women previously diagnosed with FM were recruited from the Pain and Rehabilitation Centre, a tertiary referral centre at Linköping University Hospital, Sweden. The subjects were recruited via a letter followed by a phone interview (Fig. 1). All women were between 49 and 60 years of age with a BMI of <30, in a post-menopausal state for at least 6 months, had not been using any hormonal treatments for the past 3 months and had normal mammography screenings during the preceding year. A general health examination including measurement of blood pressure, height and weight, as well as the screening of serum haemoglobin, oestradiol, follicle-stimulating hormone (FSH), tri-iodothyronine and thyroxine, cobalamin and glucose was performed. It was followed by a gynaecological examination and a clinical examination to confirm that all patients strictly met the ACR90 criteria for the diagnosis of FM [1], presenting tenderness to digital palpation with 4 kg pressure at a minimum of 11 out of 18 specific tender points, pain in all four quadrants of the body and a history of widespread pain for at least 3 months. Individuals using anti-psychotic drugs or having a history of thromboembolism, diabetes mellitus, polyneuropathy, chronic liver disease, alcohol or substance abuse, haemoglobinopathy, endometrial adenomatous hyperplasia or malignancy were not included. The presence of untreated hypertension (>160/95 mmHg) or undiagnosed vaginal bleeding also led to exclusion from the study.

The subjects who met the inclusion criteria were randomized to treatment with transdermal patches delivering either 17β-oestradiol 50 μg/day or placebo for a period of 8 weeks. The randomization was made according to a double-blind protocol administered by the local pharmacy at the Linköping University Hospital.

The study was approved by the local ethics committee at Linköping University, Sweden and the Medical Products Agency, Uppsala, Sweden (#151:662/01), and adheres to the principles of the Declaration of Helsinki. All subjects gave their written as well as oral consent to participate. They were informed that they could discontinue the study whenever they wanted and without giving any reason for their decision.

The present study is based on half of the planned sample size, calculated on a 2°C difference in cold pain threshold after treatment and 85% power. This was in turn based on the significant difference in cold pain thresholds seen after 8 weeks of HRT treatment (12.0°C vs 8.0°C; \(P < 0.05\)) in a pilot study on 13 healthy post-menopausal women, using the same testing paradigm as in the present study (Stening et al. 1999, data not published). Due to
ethical concerns arising after the clinical implementation of the results from the Women's Health Initiative study [26], restricting the use of HRT, the results were analysed when half the planned number of subjects had been studied. To get an estimate of what results could have been expected with the initially planned sample size, a theoretical duplication of the sample was made. The result of this analysis showed that further inclusion of participants increasing the total number up to the planned sample size would not yield results that were significantly different from the present results, provided that the new data exhibited a distribution pattern similar to those already obtained. We therefore decided not to include any additional subjects and closed the study.

Experimental set-up
A set of quantitative sensory tests was performed before treatment, after 8 weeks of treatment and 20 weeks after the termination of treatment. Each session took ~1 h. The experimenter was the same throughout the study. Before each session the participants completed a modified pain map (Fig. 2A), on which they marked currently painful parts of the body (divided into 36 body areas). The subjects were also prompted to note any side effects related to the treatment (i.e. hormonal or placebo). All subjects were allowed to use their daily prescribed analgesics (opiates excluded), as well as any antidepressants, but not any pro re nata medications 24 h before sensory testing.

Quantitative sensory testing (QST) was used to measure heat and cold perception thresholds, heat and cold pain thresholds, heat pain tolerance, cold pain tolerance and pressure pain threshold. Temperature thresholds and heat and cold pain thresholds were measured using computer-controlled equipment (Thermotest; Somedic, Hörby, Sweden). Measurements took place in a silent room with an ambient temperature of 21 °C, with the participants seated in a comfortable chair with the arms resting on a pillow. A Peltier element-based thermode with a surface area of 2.5 \( \times \) 5 cm and a preset temperature of 32 °C was applied first to the left and then to the right thenar region. Following a short adaptation period, the temperature of the thermode was set to increase or decrease at a rate of 1 °C/s with a cut-off limit at 5 and 52 °C, respectively, for safety precautions. The participants were instructed to press a cut-off button at the first perception of warmth or cold and at the first painful sensation induced by heat and cold, respectively. Four stimuli were given with an interstimulus interval of 4–6 s according to the method of limits [27]. The thresholds were then calculated from the average of the three most similar stimuli [28]. During measurements, no significant side difference was seen between the left and right thenar regions and the statistical analysis was, therefore, performed using the mean value of both thenar regions (based on six stimuli). Temperature and pain threshold measurements were followed by a single suprathreshold stimulus applied to
the right thenar region to measure heat pain tolerance. From a baseline temperature of 32 °C, temperature was increased with 1 °C/s until the participant pushed the cut-off button when she considered the stimulus to be intolerably painful. The apparatus was programmed to stop at 52 °C for safety precautions.

Following the tests described above, pressure pain thresholds were determined using a pressure algometer (Somedic). A 1-cm probe was applied perpendicular to the skin and pressed with an increasing force rate of 100 kPa/s to the point where the subject verbally reported it to be painful. The pressure pain threshold was defined bilaterally at 4 of the 18 tender points used in the diagnosis of FM: (i) the midpoint of the upper border of the trapezius muscle; (ii) 2-cm distal to the lateral epicondyle of the elbow; (iii) the upper outer quadrant of the gluteal region; and (iv) the medial fat pad proximal to the knee joint line. Three stimuli were applied on each site with an interstimulus interval of 2 min. The mean value of three stimuli was considered to represent the pressure pain threshold. No significant differences were seen between right and left sides, and, following a procedure similar to the procedure used in determining heat and cold pain thresholds, data from the left and right side were averaged before further statistical analysis.

Cold pain tolerance was determined using a modified cold pressor test. The participant’s left hand was immersed down to the wrist in ice-chilled water [1.5 °C (0.5)]. The water tub (2.8 l) was shaken manually by the experimenter every 30 s to avoid warming of the water next to the skin. The participant was instructed to hold the hand in the ice water as long as possible, or until a cut-off limit of 300 s was reached. The temperature in the tub was monitored with a steel probe digital thermometer (VEE GEE Scientific, Kirkland, WA, USA) and never exceeded 2 °C. When the participant withdrew her hand from the ice water, the tolerance time was noted and ratings of the perceived pain intensity were then obtained using a 100-mm visual analogue scale (VAS) anchored by no pain on the left and the most intense pain imaginable on the right.

Laboratory analyses

Venous blood samples were collected before the start of treatment and at the following test session, i.e. after 8 weeks of oestradiol or placebo treatment. Serum concentrations of 17β-oestradiol were determined by electrochemical luminescence (MedElecsys 2010; Roche, Basel, Switzerland). Initial oestradiol levels <130 pmol/l and a concurrent FSH above the normal range for women of fertile age were considered to be consistent with a post-menopausal state.

Data analysis

All statistical analyses were performed using MiniTab v.15 (Minitab Inc., State College, PA, USA) and SPSS v.12.01 (SPSS Inc., Chicago, IL, USA). A three-way analysis of variance (ANOVA) was used in which group and session were fixed factors and, in accordance with the repeated session design, person was a random factor nested within the group (treated or placebo), implying that the analysis assumes independence between the two groups while keeping track of and matching data from each person within the respective group. Furthermore, an interaction between group and session was also included in the model. In comparison between the two treatment groups at a given session, session was omitted from the
model; if applicable, Student’s unpaired t-test was used instead of ANOVA. In comparison between different sessions within each group, group was omitted from the model; if applicable, Student’s paired t-test was used instead of ANOVA. Differences between the treatment groups in hormonal levels and inclusion variables were analysed with Student’s paired t-test or Fisher’s exact test. All data sets complied with standard distribution. Statistical significance was set to $P < 0.05$.

Results

Fifteen subjects were randomly assigned to oestrogen treatment and 14 subjects to placebo. Two out of the 29 women, both randomly assigned to the placebo group, decided to withdraw from the study before the first test session, and another woman, also from the placebo group, withdrew after the second test session (Fig. 1). Details related to inclusion variables in the two groups are given in Table 1. No differences were seen, with the exception that a somewhat larger proportion of users of antidepressants were in the placebo group.

Hormonal response

Eight weeks of daily treatment with 50-$\mu$g 17$\beta$-oestradiol increased serum oestradiol levels significantly ($P < 0.01$), from a mean (s.d.) of 53 (11) pmol/l to 172 (132) pmol/l. Corresponding serum 17$\beta$-oestradiol levels in the placebo group were 56 (24) and 53 (9) pmol/l, respectively. Side effects, all well known in relation to oestrogen administration, were reported by women randomly assigned to the oestrogen treatment group, but were also seen, to a lesser extent, among women in the placebo group (Table 2). Irritation of the skin underlying the patch was reported in both groups and was probably related to the adhesive used in the patches. In one subject, randomly assigned to the placebo group, the initial hormonal levels were not consistent with a post-menopausal state and this subject was therefore excluded from the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oestradiol-treatment ($n = 15$)</th>
<th>Placebo ($n = 11$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>54.0 (3.4)</td>
<td>54.9 (3.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI</td>
<td>24.5 (3.6)</td>
<td>25.8 (2.0)</td>
<td>0.32</td>
</tr>
<tr>
<td>Years since last menses</td>
<td>4.3 (2.9)</td>
<td>4.1 (2.2)</td>
<td>0.85</td>
</tr>
<tr>
<td>S-oestradiol, pmol/l</td>
<td>53.3 (11.7)</td>
<td>52.2 (13)</td>
<td>0.81</td>
</tr>
<tr>
<td>S-FSH, U/l</td>
<td>78.9 (31.9)</td>
<td>77 (23)</td>
<td>0.86</td>
</tr>
<tr>
<td>Pain duration, years with diagnosis</td>
<td>9.0 (7.0)</td>
<td>7.8 (6.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>6 (40)</td>
<td>5 (45)</td>
<td>1.0*</td>
</tr>
<tr>
<td>Regular use of analgesics, n (%)</td>
<td>4 (26)</td>
<td>4 (36)</td>
<td>0.68*</td>
</tr>
<tr>
<td>Use of antidepressants, n (%)</td>
<td>2 (13)</td>
<td>5 (45)</td>
<td>0.09*</td>
</tr>
</tbody>
</table>

Data are given as mean (s.d.). *$P$-values were calculated using Fisher’s exact test.

Discussion

In this randomized double-blind placebo-controlled study, we conclude that 8 weeks of transdermal oestrogen treatment (17$\beta$-oestradiol 50 $\mu$g/day) does not affect the overall self-estimated pain, pain thresholds or pain tolerance in post-menopausal women with FM.

There is a lack of consensus as to which parameters should be measured when studying the effects of potential drugs in clinical trials on FM patients [29]. An efficient drug should not only induce changes in the outcome measures chosen but should also give rise to a clinically meaningful response. Dunkl et al. [30] have proposed the use of the FM impact questionnaire (FIQ) score, VAS, tender point count and total tender point pain intensity to identify responders in clinical drug trials on FM patients.

Self-estimated pain

The report on self-estimated pain, carried out before each test session using the modified pain map in which painful areas were marked, showed no significant differences between groups or between sessions (Fig. 2B).

QST

No significant differences were seen between the oestradiol-treated group ($n = 15$) and the placebo-treated group ($n = 11$ for the first two sessions, and $n = 10$ for the last session) in heat and cold perception thresholds, heat and cold pain thresholds, pressure pain threshold or heat and cold pain tolerance (Table 3). This observation was not changed by a theoretical duplication of the data.

The design of the present study was based on repeated sessions, which may give rise to session-to-session effects defined as changes in the same direction throughout all three sessions [28]. This was observed for several variables in one or the other treatment group with increasing thresholds for temperature perception, cold and heat pain and pain tolerance, and reduced thresholds for pressure pain (over one of the four tender points) and the cold pressure test, as well as increased VAS scoring of the latter (Table 3). However, no consistent pattern between groups was seen.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Oestradiol-treatment ($n = 15$)</th>
<th>Placebo ($n = 11$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast tenderness</td>
<td>4</td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Dysmenorrhoea-like pain</td>
<td>2</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>4</td>
<td>1</td>
<td>0.46</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>2</td>
<td>2</td>
<td>1.0</td>
</tr>
<tr>
<td>Depression-related symptoms</td>
<td>0</td>
<td>1</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Data are given as number of participants reporting the specified side effect. $P$-values were calculated using Fisher’s exact test.
with the FIQ score as the most responsive measure. QST or other more semi-objective methods were not included in their study, however. Previous studies have shown that QST is a reliable psychophysical method [31] and that thenar region measurements, although performed locally, accurately reflect overall pain sensitivity [32], with high method sensitivity and reproducibility [33]. Even though QST mainly measures acute experimental pain responses, experimental pain measurements, in particular those related to pressure, are significantly associated with clinical pain ratings and closely reflect the clinical status of FM patients [34, 35]. QST responses, such as those measured in this study, have been shown to be altered in FM patients, most strikingly for cold-evoked perceptions as compared with controls in multiple studies [4, 36, 37], leading to the possibility of measuring a presumed return to normal after oestrogen treatment using QST as in the present study. The current study design also offered the possibility of measuring a potential increase in pain symptoms induced by the subsequent abrupt discontinuation of oestrogen treatment [20], since QST was also performed after a 20-week washout period.

In addition to QST, the response to tonic pain was examined, using the cold pressor test. While tonic pain also can be elicited through compression-induced ischaemia, the cold pressor test has a higher degree of subject control during the procedure than methods using ischaemic pain. The cold pressor test also shows better test–retest reliability and is not potentially confounded by muscle fatigue [38]. It was hence considered to be the better test procedure considering both study design and the patient group in question. We believe that the experimental set-up used in this study, including clinical pain ratings as well as quantitative measurements of thermal and pressure pain threshold and tolerance, is not only a fairly reliable experimental method of measuring physiological responses to standardized stimuli providing a more objective outcome measure than most questionnaires and subjective scores, but also that the results obtained have a strong relation to the clinical status. With the qualification that the small sample size may have prevented the detection of subtle changes in pain perception, our data show that oestrogen treatment does not alleviate pain in post-menopausal women with FM.

Nevertheless, the present study design did not monitor potential beneficial effects of oestrogen treatment on symptoms of FM not directly related to pain. Certain psychological factors such as a passive coping style and a tendency for catastrophizing are common in women who report frequent pain [36] and FM is associated with a strong increase in comorbid anxiety and mood disorders. Given the profound effects oestrogens have on most neurotransmitter systems in the brain, other parameters such as sleep, anxiety, mood or the general quality of life may be altered by oestrogen treatment. Oestrogen treatment does indeed affect mood in some studies [39] but not in others [22], and symptoms related to depression have been shown to be associated with altered thermal pain thresholds in FM patients [36], although contradicting evidence exists [40]. Oestrogen replacement therapy also has been shown to improve sleep in post-menopausal women, in particular among those suffering from vasomotor symptoms [41], and treatment of sleep disturbances has been reported to reduce the symptoms of pain in patients with FM [42]. Additional studies on the effects of oestrogen treatment on sleep, mood and depressive symptoms in patients with FM may hence be of interest.

In the present study, the average patient had a pain duration of 8.5 years. Considering the tendency for aggravation of pain sensitivity over time in chronic pain patients

### Table 3: Temperature detection threshold, pain thresholds and pain ratings in FM patients before treatment, after 8 weeks of daily transdermal treatment with 50 μg of 17β-oestradiol or placebo and 20 weeks after termination of treatment

<table>
<thead>
<tr>
<th>Response</th>
<th>Before treatment</th>
<th>After 8 weeks of treatment</th>
<th>20 weeks after termination of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E2</td>
<td>Placebo</td>
<td>E2</td>
</tr>
<tr>
<td>Temperature threshold, °C</td>
<td>2.9 (1.3)</td>
<td>3.3 (1.5)</td>
<td>3.1 (1.4)</td>
</tr>
<tr>
<td>Cold pain threshold, °C</td>
<td>15 (7.4)</td>
<td>12.5 (4.3)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Heat pain threshold, °C</td>
<td>44.5 (3.2)</td>
<td>45 (3.1)</td>
<td>45.5 (2.4)</td>
</tr>
<tr>
<td>Heat pain tolerance, °C</td>
<td>47.5 (2.0)</td>
<td>47.5 (1.6)</td>
<td>47.5 (1.6)</td>
</tr>
<tr>
<td>Pressure pain threshold trapezius muscle, kPa</td>
<td>205 (80)</td>
<td>184 (53)</td>
<td>210 (95)</td>
</tr>
<tr>
<td>Pressure pain threshold lat. epicondyly, kPa</td>
<td>162 (65)</td>
<td>143 (35)</td>
<td>170 (73)</td>
</tr>
<tr>
<td>Pressure pain threshold gluteal region, kPa</td>
<td>273 (90)</td>
<td>238 (81)</td>
<td>264 (97)</td>
</tr>
<tr>
<td>Pressure pain threshold knee pad, kPa</td>
<td>179 (66)</td>
<td>178 (54)</td>
<td>181 (80)</td>
</tr>
<tr>
<td>Cold pressor test, s</td>
<td>35 (61)</td>
<td>23 (9)</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Cold pressor test (VAS)</td>
<td>69 (19)</td>
<td>72 (20)</td>
<td>75 (17)</td>
</tr>
</tbody>
</table>

Data are given as mean (s.d.). Two subjects (one in each group) reached the cut-off value for cold pain threshold (5°C) in each of the test sessions, and were hence ascribed this value. *P < 0.05 and **P < 0.01 compared with starting values (before treatment) in the same treatment group. No statistically significant differences were seen between treatment groups at any time point. E2: 17β-oestradiol.
due to neuronal plasticity [29], and the possible down-regulation of oestrogen receptor density after menopause as well [43], there is a possibility that oestrogen treatment at an earlier stage of the disease or for a longer period of time than in the present study might have had favourable effects. In a previous pilot study, however, 8 weeks of HRT was sufficient to induce a significant ($P < 0.05$) change in cold pain threshold in healthy post-menopausal women (Stening et al., data not published) suggesting that the presumed down-regulation of receptors does not explain the lack of effect in the present study. While the present findings show no effect of oestrogen treatment on FM, the concept that hormone-modulation treatment may be of benefit to this group of patients should nevertheless be explored further. Recent studies have shown that some other drugs acting on oestrogen-related systems do have significant effects on widespread chronic pain [44]. Myalgic pain has been shown to increase in patients receiving aromatase inhibitors [45] as well as the gonadotropin-releasing hormone agonist leuprolide [46], both inducing a reduction in serum oestradiol levels, suggesting that an effect related to oestrogens plays a role in FM and FM-like conditions. In some studies, progesterone administered in addition to oestrogen appears to decrease pain or pain sensitivity [9, 22]. On the other hand, HRT has also been associated with an increased experience of pain and pain syndromes [47, 48]. However, such observations must be interpreted cautiously, since it is possible that women who are more attentive to somatic symptoms such as pain seek medical advice more often and therefore have an increased chance of having HRT prescribed [49]. In a large survey, no significant association was seen between the use of HRT and chronic widespread pain in an unselected population [50].

**Conclusion**

Compared with a placebo, 8 weeks of transdermal oestradiol treatment does not influence pain thresholds, pain tolerance or the experience of overall bodily pain in post-menopausal women suffering from FM.

**Rheumatology key messages**

- Oestrogen substitution does not alleviate pain in post-menopausal women with FM.
- Any beneficial effects of oestrogen on FM are likely not related to reduction of pain.

**Acknowledgements**

We thank Linda Engström for help with illustrations.

**Funding**: This work was supported by the Swedish Research Council—Medicine (47879), the Swedish Brain Foundation, the Health Research Council in the South-East of Sweden and the Linneus University, Kalmar, Sweden.

**Disclosure statement**: M.H. receives remuneration for being on a scientific advisory board at Novo Nordisk, Denmark. K.G.H. has received honoraria for lectures on FM from Pierre-Fabre, Toulouse, France; Astra-Zeneca, Södertälje, Sweden; and Pfizer, Sollevantuna, Sweden. All other authors have declared no conflicts of interest.

**References**