

Editorial

Why are physicians reluctant to use estrogens for anything – or do they prefer ‘PROFOX’?

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Estrogens to physicians appear to be as garlic is to Dracula and equally illogical. The reluctance for bone physicians to use estrogens for low bone density and for psychiatrists to use transdermal estrogens for hormone responsive depression is hard to understand and is a matter of great concern. This objection is not new as it antedated the 2002 Women’s Health Initiative (WHI) study and the equally suspect Million Women Study by many years; however, these data are now used for justification for their choice of medication. Even general practitioners formerly enthusiastic about hormone replacement therapy (HRT) have been hobbled by outdated views from advisory bodies and will prescribe only for the severest of vasomotor or atrophy symptoms in the lowest dose and the shortest duration if at all.

It would seem logical that a 50–60-year-old woman with hot flushes, tiredness, depression, loss of libido, pelvic atrophy and low bone density should have estrogens in a dose appropriate for the pathology, but this is not happening. The fortunate few may have such treatment with relief of these symptoms and a substantial decrease in fracture risk as they have a 10–20% increase in bone density after 5–10 years of estrogens. But the majority of these women will either have no treatment or receive antidepressants or bisphosphonates depending on which specialist clinic she is referred to.

Selective serotonin reuptake inhibitors (SSRIs) of doubtful value are used for depression and also hot flushes regardless of their effects on libido, mental acuity, memory, general wellbeing, weight gain and the increasing problem of long-term dependency. These drugs also have a deleterious effect on bone density¹ even more than does depression untreated with SSRIs.² It is commonplace to see depressed perimenopausal women who have a longstanding history of premenstrual depression (PMS), postnatal depression (PND) who will say that they were last well without depression many years ago when they were last pregnant. They then had many months of PND and was either undiagnosed or treated with

antidepressants. The depression became cyclical as PMS as the periods returned. As they moved into their 40s, the PMS that had never been adequately treated became worse as the cyclical depression became more continuous with fewer good days a month. Being in good mood during their pregnancies followed by PND and PMS is the clue that hormonal fluctuations are a major part of the aetiology of depression in women and most importantly that elevation of plasma oestradiol levels will improve the depression in selected but many cases.³

These women respond to moderately high-dose transdermal oestradiol at all three stages of their depression; postnatal,⁴ premenstrual⁵ and perimenopausal^{6,7} but all too often they are neglected or treated with a range of antidepressants or mood-stabilizing drugs. The younger women thus suffer years of dysfunctional depression. It is astonishing how often women with a diagnosis of bipolar depression become normal when their severe PMS is treated by suppression of ovulation. Psychiatrists are not aware of the effect of estrogens on depression in spite of relevant publications of randomized controlled trials. Unfortunately, these studies have not been repeated by those most involved in the mental health of women because psychiatrists do not seem to be interested in hormonal therapy and the pharmacological companies have little desire to fund head-to-head studies of their profitable inpatient antidepressants against cheap estrogens. Women therefore suffer from this territorial conflict.

Are things better with osteoporosis? In June 2009 there is a major three-day international meeting on osteoporosis in Manchester run by the National Osteoporosis Society without a single plenary lecture on the role of estrogens. There may be a few free communications but there are no hormone companies involved and no interest from the bone physicians or rheumatologists on the scientific committee. Hence the most effective, cheapest and probably safest long-term treatment will not feature. How else will these specialists learn the simple skills of

hormone therapy? The programme committee have not responded to protests about this omission, which is the equivalent to failing to discuss angiotensin-converting enzyme inhibitors in a meeting on hypertension.

Not only do estrogens produce a dose-dependent and duration-dependent increase in bone density and bone architecture, but the cancellous bone collagen is also increased,⁸ leading to increased strength and fracture protection. It should be noted that HRT is the only treatment that has been demonstrated to produce fewer hip and vertebral osteoporotic fractures in low-risk and mid-risk women. The generalized increase in skin and bone collagen that occurs when postmenopausal women take estrogens is also seen in the intervertebral discs. The protective cushion of the discs make up 25% of the length of the vertebral column but decreases with age. Estrogens prevent this shrinkage, bisphosphonates do not.⁹

My view is that estrogens should be the first choice for the prevention and treatment of low bone density in the under 60s.¹⁰ Claus Christianson in a personal communication goes further believing that they should be the first, second and third choice in this age group. Considering the poor efficacy, long-term side effects and cost of the non-hormonal preparations, it is hard to disagree. But they may cause vaginal bleeding that seems to be another garlic moment for physicians as they feel unable to cope with it. The irony is that many bone physicians who have little knowledge of estrogen therapy would regard themselves as endocrinologists.

Bisphosphonates are now the first-line treatment in spite of increasing anxiety about osteonecrosis of the jaw,¹¹ mid-shaft femoral fractures and abnormal histomorphometric changes in the bone.¹² There is perhaps a more serious problem, if that is possible. Oesophageal and stomach symptoms are so common that 30% of women taking oral bisphosphonates require proton pump inhibitor (PPI) therapy for 'heartburn'. These are the drugs that reduce bone density and have been reported to significantly increase osteoporotic hip fractures after five years of therapy.¹³

Fosamax once weekly now in generic form is inexpensive and therefore being recommended by the National Institute of Clinical Excellence, an organization that still has not reported on HRT for the prevention and treatment of osteoporosis. The other generic preparation prescribed frequently to post-menopausal women is Prozac, which is already being used in combination with fosamax as a post-HRT nightmare, which could be called PROFOX (PROzac + FOsamaX). This substitute for estrogens would have a deleterious effect on mood, memory, libido, upper gastrointestinal symptoms requiring PPI treatment and more hip fractures with little or no improvement of the hormone responsive symptoms that trouble 50–60-year-old women. Moving from Bram Stoker's Dracula to Mary Shelley's monster, we must be beware that this created Frankenstein drug does not become a feature of the treatment of middle-aged women. In combination, PROFOX will produce more problems in combination than the individual components and either option is less effective in well-selected patients than oestradiol perhaps with the addition of testosterone and a short monthly course of a progestogen in women with a uterus.

There is no doubt that HRT is effective in reducing the number of osteoporotic fractures but is it safe? The initial 2002 WHI study reported an increase in major side-effects due to wrong patients of the wrong age given the wrong dose of an inappropriate continuous estrogen/progestogen HRT preparation. It is little consolation to stress that the investigators were informed of this about 15 years ago. However, it is now clear that this preparation caused no harm if started within 10 years of the menopause. It is also re-assuring that hysterectomized patients in this age group receiving estrogen alone have a substantial decrease in heart attacks, breast cancer and deaths,¹⁴ although the study of this age group was discontinued prematurely without significance being confirmed or otherwise.¹⁵ No convincing explanation has been given.

The increasing awareness of the safety of HRT on the cardiovascular system as featured in a IMS meeting in January is discussed by Stevenson in an accompanying editorial in this edition of *Menopause International*.¹⁶

Q1

Competing interests:

Q2

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