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'PROFOX' – the post HRT nightmare

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ABSTRACT

The recent report of a two-fold increase in esophageal cancer in women taking oral bisphosphonates is yet another reason to question current relegation of hormone replacement therapy (HRT) to a minor role in the correction of many problems occurring in the younger postmenopausal woman. Women under the age of 60 years with low bone density, flushes, sweats, vaginal dryness, loss of libido and climacteric depression would be treated with estrogens by gynecologists and most general practitioners. It is regrettable that bone physicians use bisphosphonates as first-line therapy in this age group, in spite of the growing number of serious complications reported. Similarly, psychiatrists have little experience in the use of estrogens for the reproductive depression syndrome of postnatal depression, premenstrual depression and perimenopausal depression, but use antidepressants. The adverse effects reported in the 2002 Women's Health Initiative study are given as justification for not using estrogens, although serious complications did not occur in women starting HRT before the age of 60 years. But, in reality, the objection to estrogens from psychiatrists and bone physicians preceded this study by decades and was a result of their unfamiliarity with this treatment. Regrettably, PROFOX (PROzac + FOsomaX) will become an established treatment for women who really need estrogens.

OSTEOPOROSIS

A nightmare of the future is that postmenopausal women with hot flushes, depression, sexual problems and low bone density, who need estrogens perhaps with testosterone, will be given a selective serotonin reuptake inhibitor (SSRI) and bisphosphonate combination, PROFOX, a Frankenstein combination of PROzac and FOsamaX. As these two drugs are now available as cheap generics, they are already being prescribed together. The problem is that, individually or in combination, they are often less effective and produce more side-effects than estrogens used in the appropriate age group. Unless the regulatory authorities consider the current safety data in the under-sixties and modify their resistance to hormone replacement therapy (HRT), the spectre of PROFOX will be upon us. It is a vision of the future which should be avoided.

Physicians and psychiatrists have been slow to accept the clear benefits of estrogen therapy in the treatment of osteoporosis and depression. Is it an honest fear of side-effects, ignorance of hormone therapy, and misinterpretation of the data, or simply a territorial hold on the condition which then condemns women to suboptimal therapy?

The side-effects of the non-hormonal treatments for osteoporosis are now becoming apparent. The tragedy for women is that estrogens are certainly more effective in protecting the skeleton and disc, cheaper, long-lasting, safer in the early postmenopausal years, but they are not being used.

Although estrogens have been proven to prevent fractures in a mixed risk population[1] and the benefits on bone density and histology are dose-dependent[2], it has been relegated to a treatment to be used only if others fail or if the woman has severe menopausal symptoms. Estrogens have an anabolic effect on collagen which protects not only the cancellous bone of the skeleton but also the intervertebral discs which make up one-quarter of the length of the spinal column[3,4]. This latter benefit is not produced by bisphosphonates. The failure of physicians to familiarize themselves with estrogen therapy has, in their minds, been justified by the results of the Women's Health Initiative (WHI) study and by the regulatory bodies who have advised that estrogen should not be first-choicetherapy for osteoporosis. However, the physicians' objections to estrogen therapy antedated the WHI study by many years and are

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COMMENTARY

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the result of lack of knowledge of the subtleties of the use, the dose and route of administration of various estrogens, gestogens and, occasionally, androgens.

The complications of estrogen and progestogen therapy occur mostly in women who started this therapy 20 or more years after the menopause[5]. Updated information and interpretation of the WHI study indicate that HRT, particularly estrogen alone, is both safe and protective in the younger postmenopausal woman below the age of 60 years[6]. Such therapy is associated with fewer fractures and less colon cancer. There is also a non-significant reduction of 42% in heart attacks (hazard ratio (HR) 0.3–1.03), of 28% in breast cancer (HR 0.43–1.07) and 27% fewer deaths (HR 0.47–1.13)[6]. It remains a mystery why this arm of the study was discontinued prematurely.

In the opinion of many workers, estrogens should be the first-line therapy in this age group[7]. However, Fosamax Once Weekly is an inexpensive alternative recommended by the National Institute for Health and Clinical Excellence and preferred by physicians. It confers fewer skeletal and systemic benefits than estrogens but it does not confuse the medical attendant with hormonal side-effects such as bleeding, mastalgia and occasional symptoms of premenstrual syndrome. These are problems that can be dealt with by any competent general practitioner but have not yet been learned by most specialist bone physicians and rheumatologists, who also seem to be complacent about the considerable long-term side-effects of bisphosphonates. These include osteonecrosis of the jaw, abnormal bone histology and mid-shaft femoral fractures[8], and a doubling of the incidence of esophageal cancer[9]. With the more common problem of esophageal ulceration by bisphosphonates, there is an increasing need for proton pump inhibitors, with their own detrimental effect on bone density[10].

Bone physicians frequently justify their treatment preference with the belief than any benefit on the skeleton from estrogens disappears when hormone therapy is discontinued. Not only is this contrary to experience and logic, but this view has been shown to be false in the prospective long-term data from four trials showing a long-lasting antifracture effect[11].

DEPRESSION

A similar 'turf war' occurs with the commonplace depression in perimenopausal women. These women with estrogen-responsive depression[12] often have a history of postnatal depression and premenstrual depression, which have all been shown to be effectively treated by transdermal estrogens in good, controlled trials[13–15]. It is, therefore, surprising that none of these studies have been repeated by psychiatrists – those mostly responsible for the treatment of depression in women. There has never been a head-to-head study of antidepressants against estrogens. This neglect is either due to the unlikely belief that these original studies are regarded as perfect or because psychiatrists and the pharmaceutical industry do not want to show the benefits or even the superiority of estrogens. For example, there is only one placebo-controlled study of transdermal estrogens in severe premenstrual depression[14], but there are now 50 recent, similar studies showing that SSRIs are useful. Why should the pharmaceutical industry fund studies that reveal that their high-profit, in-patent antidepressant is less effective than the much less profitable estrogens?

Psychiatrists refuse to accept these data which demonstrate the value of estrogens in certain forms of depression in women, instead relying upon psychotherapy, SSRIs and even electroconvulsive therapy. The number of women, particularly 45-year-old, middle-income, white women taking SSRIs has increased four-fold in the last 10 years[16]. The side-effects, such as loss of libido, are considerable and a 45% increase in heart attacks and stroke, with a 100% increase in hemorrhagic and fatal stroke, has been reported in women taking SSRI or tricyclic antidepressants[17].

Once again, it is to the disadvantage of the women that psychiatrists have not chosen to become aware of treatment of certain common types of depression by hormones. It is commonplace to see women with perimenopausal depression who have been taking many antidepressant and mood-stabilizing drugs for 10–20 years. The clue to whether they have a hormone-responsive depression is in the history and cannot be established by hormone assays. They usually have a long history of premenopausal depression and enjoy good mood during pregnancies, often followed by postnatal depression. They usually claim to have been last well during their most recent pregnancy, after which they started or were recommenced antidepressants for postnatal depression, later developing into premenstrual depression as the periods return, and finally climacteric depression[18]. It is difficult to obtain precise data, but antidepressants are now used by about 15% of women in the UK and the USA[16]. There is even a move to use SSRIs for the treatment of vasomotor symptoms[19]. It is barely effective but it is becoming a new indication for SSRI therapy and another excuse not to use estrogens.

The result is that women are currently being treated with years of barely effective, habituating, multidrug therapy, producing profound personality changes, loss of libido, weight gain and anxiety. Those women who are still having ovarian cycles often have cyclical symptoms, with up to 12 good days a month and then can and do suffer the misdiagnosis of bipolar disorder and the severe long-term side-effects of mood-stabilizing drugs.

CONCLUSION

We need the advisory bodies to consider the revised conclusions of the WHI study in this age group and

support the logical use of estrogens under the age of 60 years. Women also need physicians to overcome their antiestrogen instincts and learn the simple skills of using HRT. Otherwise, PROFOX or worse is inevitable.

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