

Drug information needs clarification

I read with great consternation the article "Raloxifene. Not better than estrogen,"¹ translated from the French *La revue Prescrire*.² As an article in a journal that is designed to keep Canadian family physicians up-to-date on the latest medical information, it leaves much to be desired. Without going into great detail, below is an outline of the most recent, evidence-based information on raloxifene, in particular, as it compares with estrogen. For more details, I refer readers to a review article³ on raloxifene, published in another Canadian peer-reviewed journal.

1. In Canada, raloxifene (eg, Evista) is indicated for preventing and treating osteoporosis in postmenopausal women. Data to support this indication come from the MORE study (Multiple Outcomes of Raloxifene Evaluation).⁴ This was a double-blind randomized placebo-controlled study of 7705 postmenopausal women with osteoporosis. It demonstrated that, after 3 years of therapy, raloxifene reduced the incidence of new vertebral fractures by 55%. Raloxifene also reduced the incidence of new vertebral fractures in women with pre-existing vertebral fractures by 30%. The 4-year data from the MORE study were presented at the American Society for Bone and Mineral Research meeting in Toronto, Ont, and are almost identical to the 3-year results.⁵

The MORE study is the first adequately powered, randomized placebo-controlled trial to demonstrate that an estrogenlike agent reduces the risk of new vertebral fractures.⁶ This is level 1 evidence. There are no comparable

data on the ability of estrogen to reduce fractures. The evidence for estrogen to reduce fractures is level 3 only, from observational studies and from one small (n=75) randomized, prospective study of the 100 µg estradiol patch.

2. There is no evidence from randomized, prospective studies that estrogen reduces cardiovascular disease. In fact, recent studies^{7,8} suggest the opposite, at least for secondary prevention. Both estrogen and raloxifene reduce a number of surrogate markers of cardiovascular risk, although they each have their own unique profiles. Studies are under way to

determine whether raloxifene will affect cardiovascular events.

3. It is well-known that the use of unopposed estrogen results in uterine stimulation, necessitating the concomitant use of progesterone. In fact, more recent evidence shows that the use of progesterone does not completely negate the potential stimulatory effects of estrogen.⁹ Raloxifene has been shown in numerous studies to have an antiestrogen effect on the uterus, with no evidence of uterine stimulation and no need to use concomitant progesterone.^{9,11}
4. Numerous studies have revealed a slightly increased risk of breast cancer with estrogen use, with a more recent study suggesting the concomitant use of progesterone increases the risk further.¹² The MORE study has demonstrated a 76% reduction in the incidence of new invasive breast cancers with raloxifene compared with placebo, not 1% as indicated in the article.¹³ This is by no means sufficient to support an indication for raloxifene for preventing breast cancer, but it shows a safety profile for raloxifene superior to that for estrogen.
5. Raloxifene does not treat hot flashes associated with menopause. In fact, in the MORE study, incidence of hot flashes while using raloxifene was 9.7% compared with 6.4% while using placebo. Estrogen remains the treatment of choice for hot flashes associated with menopause. Raloxifene should not be used to treat hot flashes in symptomatic early postmenopausal women.
6. The issue of ovarian cancer, which was raised by a few poorly informed individuals when raloxifene was first introduced to the market, has been shown to be completely unfounded.

Make your views known!

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Faites-vous entendre!

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Letters ♦ Correspondance

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The discovery of ovarian tumours in rodents that were given raloxifene for their entire reproductive lives, when their ovaries were susceptible to hormonal influences, is in no way similar to the situation in postmenopausal women, whose ovaries no longer respond to hormonal changes. Furthermore, the more common types of ovarian tumours in humans are adenocarcinomas, which are not responsive to hormonal changes, while ovarian tumours in rodents are. As well, the MORE study and others have been tracking the incidence of ovarian cancer, and there is no indication whatsoever of an increased risk of ovarian cancer with the use of raloxifene. There is no reason to “watch the ovaries” with raloxifene.

7. Raloxifene was not “obtained by chemical operation on tamoxifen” as stated in the article. Tamoxifen is a triphenylethylene compound, and raloxifene is a benzothiophene, a completely different and distinct chemical entity.
8. Hyperglycemia was not observed with greater frequency in the raloxifene group than in the placebo group in the MORE study, as reported in the article. The self-reported incidence of diabetes was greater in the raloxifene groups than in placebo groups, but these reports were not substantiated by glucose levels. In fact, glucose levels and HbA_{1c} were similar in the placebo and raloxifene groups.

The article published in Canadian Family Physician was not only a review of very old data, it contained many inaccuracies and misrepresented the data on raloxifene today.

—Loren D. Grossman, MD, FRCPC, FACP
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Research
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by mail

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Response

We consider that our account of the results of the MORE trial is correct. Our wording was more precise than that used in your letter, which argues in terms of the relative risk, exaggerates the effect rather than the absolute risk, and gives a more realistic notion of the true benefit. You state that the benefit is 55% in terms of the incidence of a first vertebral collapse, whereas we wrote that, in the clinical trial, 2.6% of women using raloxifene had at least one vertebral collapse, compared with 4.5% of women using placebo (a benefit of only 1.9% in absolute values).

We recently reviewed the various consensus statements^{1,2} and expert recommendations on fracture prevention in

elderly women. All consider estrogen as the first-line drug. Health professionals are therefore right to wait for the results of trials comparing raloxifene with estrogen on the basis of clinical end points. The only trial available was unfavourable to raloxifene in terms of mineral bone density, a surrogate end point.

No one denies that the level of evidence is low. However, your references are incomplete. The trial involving 75 women concerned secondary prevention. You also fail to mention a placebo-controlled trial of transdermal estradiol in primary prevention, which involved 123 women treated for 2 years. We reviewed³ this trial in a previous article.

We did not state that estrogen reduces cardiovascular risk. We simply reported on changes in cholesterol levels on estrogen and raloxifene.

Letters ❖ Correspondance

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Regarding endometrial cancer, our article does not deny the lower incidence using raloxifene relative to estrogen, but we were unable to find any data on the real benefit in absolute values.

Your statement that the risk of breast cancer is reduced by 76% on raloxifene is highly misleading, as it is again based on the relative risk. The figures are 13 cases using raloxifene and 27 using placebo, or incidence rates of 0.3% versus 0.7%, as we stated.

We agree that raloxifene increases the frequency of hot flashes, unlike estrogen. We stated that data on ovarian cancer in animals cannot be extrapolated to humans. Nevertheless, these data should not be overlooked. The possible risk of an increase in ovarian cancer can be ruled out only by close scrutiny of drugs.

The relation between raloxifene and tamoxifen is indicated in the report⁴ by

the European Agency for the Evaluation of Medicinal Products. It also appears in *Martindale—the Complete Drug Reference*.⁵

The report of the MORE trial indicates a higher frequency of aggravation of pre-existing diabetes, or onset of diabetes, in patients using raloxifene than in those using placebo.

We fail to see why you accuse us of using old data. We reported the results of the MORE trial available in May 1999 and updated our article to July 2000 (when the 3-year results of this trial were available). Our literature search is explicit and up-to-date.

We see no reason to modify our stated judgment on raloxifene.

—Dr Bruno Toussaint
Editor-in-chief
La revue Prescrire
Paris, France

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Dr Fred Fallis

It is with great sadness that I read¹ of the passing of Dr Fred Fallis. I was a locum tenens in Fred's practice in North York, Ont, from 1970 to 1973 and *what* a general practice it was!

We would run back and forth from the emergency room, the family practice clinic, the St George St Outreach Clinic, or a meeting at the old Toronto General Hospital, back to Fred's office on Avenue Rd. Several times I dropped in for supper