moral development call for some clarification.

First, it is unclear why the authors calculated a weighted score based on the students' responses. The most substantial evidence presented for the assertion that moral reasoning declined over the study period was the small but "statistically significant" changes in weighted scores, but the change for the total group was only 17.98 points (out of a possible 450). Does this small change really represent a significant difference in students' moral reasoning abilities?

Second, the authors argue that a lack of improvement in moral reasoning is of concern, and their concluding paragraph indicates a belief that ideally students' moral reasoning skills should increase through their medical education experience. However, many students come to medical school with significant life experience and have already completed advanced degrees. At what point can they be expected to attain the highest stage of moral reasoning that they will achieve?

Finally, although the moral reasoning of students who started at a higher stage declined, that of students starting at a lower stage improved. This finding could be interpreted positively: those who needed improvement most did improve. It also seems odd that the students who were the most morally mature would be most adversely affected by the medical school experience.

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Osteoporosis guidelines

The *CMAJ* supplement containing clinical practice guidelines for osteoporosis[1] is a valuable document. However, I find it difficult to understand why raloxifene has been classified as a first-line therapy for the prevention of further bone loss (in postmenopausal women with low bone density) and for the treatment of osteoporosis, given that it has not been shown to significantly reduce the occurrence of hip fractures.[2,3] Moreover, in the Multiple Outcomes of Raloxifene Evaluation (MORE) study,[2] the incidence of venous thromboembolism was 1% among patients treated with this drug. In my own experience of prescribing this drug for approximately 200 female patients, 2 elderly women with no other known risk factors experienced pulmonary emboli during the first year of treatment, and a third elderly patient was referred to me when deep venous thrombosis developed 1 month after raloxifene was substituted for estrogen therapy.

I feel that the osteoporosis guidelines do not adequately convey the magnitude of the risk for venous thromboembolism during raloxifene therapy. This risk is reported as 3.32 events per 1000 person–years of treatment,[1] but because most raloxifene-related events of this type occur during the first year of treatment,[4] the risk will appear lower as the duration of follow-up increases. In women under 60 years of age, the risk seems to be low: only 1 case occurred in 859 women treated for 3 years at doses of 30 to 150 mg/day.[5] If this is so, the risk in older women may be even higher than the 1% reported in the MORE study.

I am concerned that the designation of raloxifene as a first-line therapy may lead to its being prescribed even when a safer and more effective drug such as alendronate or risedronate would be more appropriate. In women over the age of 60, raloxifene should be used with caution and only after the patient has been informed of the magnitude of the risk for venous thromboembolism (at least 1 in 100).

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In most respects, the guidelines for the diagnosis and management of osteoporosis, developed by the Osteoporosis Society of Canada,[1] are excellent. However, they suffer from 2 serious deficiencies.

First, all descriptions of the benefits of therapy are provided as relative risk reductions, with no mention of absolute risk reductions or numbers needed to treat (although, interestingly, the small increase in venous thrombosis associated with use of raloxifene is described as an absolute risk).[1] From a clinical point of view, absolute benefits and risks markedly influence therapeutic decisions. This is particularly important in the prevention and treatment of osteoporosis, because the risk of fracture without therapy varies so much with the patient's characteristics. Groups such as the American College of Physicians Journal Club mandate that both absolute and relative risk reductions be provided when describing the benefits of a therapy.[2] I am surprised that *CMAJ* does not have a similar policy.

Second, the guidelines make no mention of cost-effectiveness. I believe that cost-effectiveness should be mentioned for any guidelines that could affect the

medical management of a large number of Canadians. In my experience, these guidelines are now being used by clinicians and pharmaceutical companies to convince those who pay for osteoporosis drugs to loosen their restrictions on reimbursement. Because most payers consider cost-effectiveness as well as medical effectiveness, the guidelines would be more influential if they provided good evidence of cost-effectiveness.

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[One of the authors responds:]

Although raloxifene has been shown to have positive effects on bone mineral density[1] and in the prevention of vertebral fracture[2] in postmenopausal women with osteoporosis (with or without pre-existing vertebral fracture), there are as yet no data demonstrating efficacy for the prevention of hip fractures in this population. Furthermore, alendronate and risedronate have been shown to prevent hip fractures only in elderly postmenopausal women with severe osteoporosis (with pre-existing vertebral fracture).[3,4] No adequately powered trial has yet been completed to address the impact of raloxifene on hip fracture. As stated in the 2002 guidelines,[5] "a recommendation that a specific therapy be used as 'first-line' therapy for osteoporosis relies on Level 1 evidence for prevention of fragility fracture (mainly vertebral fracture)," and raloxifene fulfills this criterion.

In the MORE study,[2] the administration of raloxifene (60 mg/day) in postmenopausal women increased the risk of venous thromboembolic events from 1.44 to 3.32 events per 1000 woman-years (change in absolute risk from 0.5% to 1.1%; attributable risk 0.6%) over 40 months (relative risk compared with placebo 3.1%, 95% confidence interval 1.5% to 6.2%). Edmund Yendt's clinical experience (2 cases of venous thromboembolism among 200 patients given raloxifene) is compatible with these data, but one must be wary of reporting clinical data when obtained from a small sample of patients, since the smaller the sample size, the greater the chance of drawing an incorrect conclusion. In the trial by Johnston and others,[6] cited by Yendt, the rates of venous thromboembolism and pulmonary embolism were not expressly reported; rather, only the rates of deep vein thrombosis were given. Therefore, it is impossible to compare these findings with those of the MORE study[2] (which reported both deep vein thrombosis and pulmonary embolism as venous thromboembolism). As stated in the 2002 guidelines,[5] venous thromboembolism constitutes a serious side effect associated with raloxifene, although it is reported infrequently and the magnitude of the risk is similar to that observed for both hormone replacement therapy and tamoxifen. We agree that this risk should not be taken lightly, but it does not outweigh the benefits of raloxifene as a first-line treatment for postmenopausal women with osteoporosis.

Andreas Laupacis has cited 2 serious deficiencies in the guidelines: the lack of mention of absolute risks and the lack of cost-effectiveness analyses. We agree that discussion of absolute risk, absolute risk reduction and its reciprocal, the number needed to treat, could have made the guidelines stronger. However, the data from most of the prospective trials evaluating efficacy of therapy in preventing fracture are provided as relative risks in populations with high absolute risk at baseline; therefore, the absolute risk would not provide stronger antifracture evidence than that supplied by the relative risk in these known high-risk populations. Furthermore, evidence-based guidelines are not review articles or meta-analyses and do not pretend to compare various drug therapies in terms of a specific outcome, such as antifracture efficacy. This type of comparison can only be achieved in head-to-head randomized controlled trials.

With regard to the cost-effectiveness of therapies, it was decided in 1998, when development of the 2002 guidelines[5] began, not to include cost-effectiveness questions. This decision was based on a number of factors, including lack of available high-quality economic impact data for all therapies (especially from Canada), the number of questions already being posed for the guidelines and the perceived priority of the need to determine the most effective therapies, irrespective of cost. As Laupacis has pointed out, the adoption of many of these therapies by third-party payers may require positive cost-effectiveness data, but our goal was to provide a true evidence-based guide to clinical efficacy. We hope that some of Canada's excellent health economists will pick up where we left off and supply this important cost-effectiveness information.

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