

diabetes may be asymptomatic. Once complications emerge, the prevalence and risk of depression climbs. Brown and colleagues' findings remind us that we should focus our attention among patients newly diagnosed with diabetes on prevention of complications, while at the same time remaining sensitive to the risk of depression if, despite all efforts, complications of diabetes develop.

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# Clinical practice guidelines for the use of parathyroid hormone in the treatment of osteoporosis

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In 2002, Osteoporosis Canada published clinical practice guidelines for the diagnosis and management of osteoporosis in Canada.<sup>1</sup> At the time, there was considerable evidence for the use of anti-resorptive agents in the management of osteoporosis, including estrogen, the selective estrogen receptor modulator, raloxifene, several approved bisphosphonates (alendronate, etidronate and risedronate) and calcitonin. For these agents, much information exists to document their primary efficacy in preventing fractures, the most important outcome of osteoporosis.

In contrast to anti-resorptive drugs, anabolic agents result in the formation of new bone in both trabecular and cortical envelopes and thus partially repair the deterioration in micro architecture that leads to the increased fragility of adult osteoporotic bone. Sodium fluoride was the first of such agents to be evaluated in randomized controlled trials, but the results showed that the bone of patients receiving the drug was of poor quality and that the incidence of fractures was not reduced even though large measurable increments in bone mineral density (BMD) were seen. In the 2002 guidelines, parathyroid hormone (PTH) was mentioned only briefly because the

pivotal phase III trial of teriparatide (PTH[1-34]) had only just been published,<sup>2</sup> and regulatory approval for its clinical use had not yet been obtained in Canada.

Osteoporosis Canada updates its clinical guidelines at intervals, when a sufficient body of evidence becomes available to allow a considered interpretation of the place new therapies should occupy in the management of osteoporosis. It has now been possible for the Clinical Guidelines Committee of Osteoporosis Canada to perform a systemic review of trials evaluating PTH for the treatment of osteoporosis. Its findings appear in this issue of *CMAJ* (see page 52).<sup>3</sup> Both the systematic review and the recommended guidelines were reviewed by the Scientific Advisory Council of Osteoporosis Canada (members of which include primary care physicians), together with a panel of patients with osteoporosis. Teriparatide has been most widely used. There is only limited information on the full sequence hormone PTH(1-84), given that the results of the phase III antifracture trial have yet to be published in full. Another analogue, cyclic PTH(1-31) amide, is currently undergoing phase II evaluation.

The systematic review was undertaken to review studies of the efficacy and safety of PTH for the treatment of osteoporosis in men and postmenopausal women and of osteoporosis caused by glucocorticoids. The primary search focused on outcomes that included either BMD or fractures. Secondary outcomes were back pain and quality of life. There was level 1 evidence that teriparatide treatment for 21 months resulted in significant reductions in both vertebral and non-vertebral fractures in postmenopausal women with previous vertebral fractures. Consistent with its anabolic action, teriparatide and intact PTH significantly increased BMD at all skeletal sites except the radius (level 1 evidence). There were initial concerns that the neutral effects of PTH on radial BMD might translate into increased fragility of tubular long bones, but these have not been realized. PTH leads to periosteal new bone formation along the outer cortical surfaces of long bones. According to biomechanical theory, small increments in the external diameter of a cylindrical structure translate into marked increments in mechanical strength. This is consistent with the findings of the reduced incidence of nonvertebral fractures seen in the phase III RCT of teriparatide.<sup>2</sup>

There remain a number of important issues surrounding the use of PTH and its interactions with bisphosphonates. First, PTH has not yet proven to be more effective than bisphosphonates in reducing incident osteoporotic fractures during adequate head-to-head comparator trials. Thus far, the only head-to-head trials have been small comparisons between teriparatide and alendronate, and they have shown a greater efficacy on BMD and a trend toward improved fracture incidence in favour of teriparatide. Table 1 summarizes the historical antifracture efficacy of teriparatide and the 2 most commonly used bisphosphonates in Canada, alendronate and risedronate.<sup>2,4-7</sup> Second, prior or concurrent use of alendronate appears to diminish the increments in BMD and biochemical markers of bone turnover induced by teriparatide. Until this interaction is clarified, the optimal use of teriparatide should be in bisphosphonate-naïve patients. This is a dilemma for insurers, who typically require failure of less

expensive treatments before considering coverage of more expensive options.

Since teriparatide's approval in Canada in June 2004 for the treatment of osteoporosis, its uptake has been slow. In 2005, the number of prescriptions for teriparatide accounted for less than 1% of all prescriptions for drugs used in the treatment of osteoporosis. In large part, this may be due to lack of formulary access and the high cost of the therapy. In Canada, treatment with teriparatide is limited to a maximum of 18 months, in part because of carcinogenicity studies demonstrating an increased incidence of osteosarcoma in rats treated from "adolescence" through to senescence. The current direct medication cost for an 18-month course of teriparatide is \$15 875, although the manufacturer has recently introduced a discounted pricing system available to patients with limited ability to pay for their own drug supply. In December 2004, the Canadian Expert Drug Advisory Committee recommended that provinces not include teriparatide in their formularies because of the high cost of treatment and the lack of a convincing cost-utility analysis to justify its inclusion.<sup>8</sup> At the time of writing, there was no access to teriparatide under any of the provincial formularies except in Quebec. The objectives of the systematic review of PTH conducted by Osteoporosis Canada did not include a review of cost-utility analyses, but it is appropriate to take these realities into account in formulating our guidelines.

One way to compare the cost-effectiveness of osteoporosis therapies is to determine the number needed to treat (NNT) to prevent a fracture. Table 1 shows the historical antifracture efficacy of teriparatide and the 2 most widely used bisphosphonates, alendronate and risedronate, as reported in the primary phase III clinical trials of each drug. These data are not derived from head-to-head comparisons. They were taken from RCTs involving postmenopausal women who had at least 1 prevalent vertebral fracture. In the 4 trials cited, the mean age of the study cohorts ranged from 69 to 71 years and treatment duration from 21 months (teriparatide) to 3 years

**Table 1:** Comparison of fracture risk reduction between teriparatide therapy (for 21 months) and therapy with commonly used bisphosphonates (for 36 months) in clinical trials involving postmenopausal women with at least 1 baseline prevalent vertebral fracture\*

Outcome	Teriparatide <sup>2</sup>	Alendronate <sup>4</sup>	Risedronate <sup>5</sup>	Risedronate <sup>6</sup>
<b>New vertebral fractures</b>				
Relative risk (95% CI)	0.4 (0.2-0.6)	0.5 (0.4-0.7)	0.6 (0.4-0.8)	0.5 (0.4-0.7)
Placebo incidence rate, %	14	15	16	29
Absolute risk reduction, %	9	7	5	11
NNT	11	9	20	10
<b>New nonvertebral fractures</b>				
Relative risk (95% CI)	0.5 (0.3-0.9)	0.8 (0.6-1.0)	0.6 (0.4-0.9)	0.7 (0.4-1.0)
Placebo incidence rate, %	6	15	8	16
Absolute risk reduction, %	3	3	3	5
NNT	34	34	43	19

Note: CI = confidence interval, NNT = number needed to treat.

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(alendronate and risedronate). Although there may have been other factors influencing future fracture risk, the 4 study populations are comparable. In the absence of head-to-head trials, this is a pragmatic way to compare efficacy, because age and the prevalence of fractures before initiating therapy were primary determinants of fracture rates and therefore greatly influence the NNT. As can be seen in Table 1, the apparent relative efficacy of teriparatide and bisphosphonates is similar in this population. However, we believe that simple comparisons of NNT calculations should not be the only criterion by which to compare the benefits of teriparatide with bisphosphonates, especially in this case in which the underlying fracture risk in the RCT of teriparatide may in fact have been much higher, and the duration of treatment much shorter, than that in the RCTs evaluating alendronate and risedronate; both factors may have obscured the superiority of teriparatide over these bisphosphonates.<sup>9</sup>

The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has compared the cost-utility ratios between the bisphosphonates, raloxifene and teriparatide using a modified individual Markov approach. The baseline model examined the cost-utility ratio of these agents in postmenopausal women with at least 1 prevalent vertebral fracture and a T-score of less than -2.5, stratified by ages 50 through 80 years. The modelled risk was adjusted for the severity of underlying osteoporosis, such that patients with either (a) 2 or more fractures, a T-score of less than -3.0 and an additional major but nonmodifiable risk factor or (b) an "extremely" low T-score of less than -4.0 would have a 4-fold higher risk of fracture than that expected of the baseline model. For simplicity, Table 2 outlines the cost-utility ratios (calculated in pounds sterling per quality-adjusted life-year [QALY]) to prevent 1 clinical fracture in a postmenopausal woman treated with either teriparatide or alendronate.<sup>10</sup> As can be seen, the cost-utility ratio becomes more favourable when treatment is given to older patients, and the ratio for teriparatide approaches that for alendronate only among women at 4-fold increased risk of incident frac-

tures. The NICE analysis has the advantage that generally agreed on quantifiable risks and benefits were applied within a single health care system (the United Kingdom); the much higher cost-utility ratio for teriparatide as compared with the ratio for the bisphosphonate is driven by the high cost of teriparatide rather than its efficacy. However, in the absence of head-to-head fracture trials, this analysis may well underestimate the potential superiority of teriparatide over bisphosphonates.

## Recommendations

On the basis of these considerations, the Clinical Guidelines Committee of Osteoporosis Canada suggests the following recommendations for the use of teriparatide, recognizing that these may or may not be applicable to the use of other PTH analogues as more data become available. The grading of recommendations involved the use of consensus techniques with a panel of expert consultants and followed the same grading technique used in the 2002 clinical practice guidelines.<sup>1</sup> Recommendations were assigned a grade of D if they were based only on a committee consensus in the absence of clear supporting evidence or when the evidence was weak. All recommendations were reviewed by the guidelines committee, and if appropriate, the assigned level of evidence or grade of recommendation was modified.

- On the basis of fracture efficacy data, teriparatide should be recommended as a first-line therapy for women 65 years or older who have prevalent vertebral fractures and low BMD (T-score  $\leq -2.5$ ) (grade A). Given the evolving evidence that bisphosphonates might blunt the effectiveness of teriparatide, patients selected for treatment should ideally be bisphosphonate-naïve (grade B).
- On the basis of the results of a cost-effectiveness study, teriparatide should be reserved for the most severely affected patients (those with more than 1 fragility fracture and very low BMD) (grade B). Until there is direct comparative evidence that teriparatide has superior antifracture efficacy to bisphosphonates, the latter are a more appropriate initial choice for patients with less severe osteoporosis (grade D).
- Other potential candidates for teriparatide include postmenopausal women with very low BMD (T-score  $\leq -3.5$ ) and those who continue to have fragility fractures despite an adequate trial of bisphosphonates (2-year period) (grade D).
- Teriparatide should be considered as a second-line therapy for men 65 years or older who have severe osteoporosis and prevalent fragility fractures (grade B) or patients who are taking long-term corticosteroid therapy and have corticosteroid-induced osteoporosis and prevalent fractures (grade D).
- On the basis of BMD outcomes, it is recommended that alendronate (grade B) and probably other bisphosphonates (grade D) should be discontinued before starting therapy with teriparatide. There is no evidence on whether there should be a washout period.
- Therapy with an anti-resorptive agent after completing

**Table 2:** Cost-utility ratios to prevent 1 clinical fracture in a postmenopausal woman prescribed either teriparatide or alendronate (the NICE model)\*

Drug; patient age	Cost per QALY, £	
	Baseline risk	4-fold incremental risk†
<b>Teriparatide</b>		
60 yr	> 100 000	48 500
70 yr	> 50 000	18 300
<b>Alendronate</b>		
60 yr	36 600	< 15 150
70 yr	12 200	< 12 200

Note: NICE = National Institute for Health and Clinical Excellence.

\*Cost per quality-adjusted life-year (QALY) spent to prevent 1 incident fracture due to osteoporosis, at costs prevailing in the United Kingdom in 2003/04.<sup>10</sup> Costs are in pounds sterling (1 £ = Cdn\$ × 2.1, as of May 2006).

†Women at 4-fold increased risk of incident fractures.

teriparatide therapy is recommended to maintain or increase BMD (grade B).

- Baseline serum levels of calcium, PTH, uric acid, creatinine and 25-hydroxyvitamin D [25(OH)D] should be measured — and confirmed to be within acceptable normal limits — before therapy with teriparatide is started. Serum calcium levels should be measured again — before injection — after the first month of therapy, since mild hypercalcemia will develop in a minority (about 10%) of patients during treatment. Hypercalcemia can usually be managed by reducing the intake of oral calcium supplements and, if necessary, by reducing the teriparatide injection frequency to alternate days (grade D). In patients with a history of renal stones, calcium levels in 24-hour urine collections should be measured (grade D).
- The duration of teriparatide therapy should be limited to a maximum of 18 months because of the lack of long-term safety data (grade D).
- Supplemental calcium intake should be limited to 500 mg/d to minimize the risk of hypercalcemia. Vitamin D supplements of 800 IU/d are particularly important in preventing subclinical vitamin D deficiency during teriparatide treatment (grade D).
- Use of teriparatide is contraindicated in children and adolescents and in people with a history of skeletal irradiation or Paget's disease, or both (grade D).
- Teriparatide should be avoided in patients who have primary hyperparathyroidism or who have significant renal impairment or vitamin D deficiency. It should be used with caution in people with a history of gout (grade D).

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