Bisphosphonates and Teriparatide for the Prevention of Osteoporotic Fractures in Postmenopausal Women
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Technology and Condition
Bisphosphonates (etidronate, alendronate, risedronate) and teriparatide for the prevention of fracture in postmenopausal women.

Issue
Osteoporosis is associated with significant disease burden. Effective therapies for osteoporosis are attractive because their acquisition costs may be offset by future savings associated with fracture prevention. There is a need to assess the value in funding these drugs, given their considerable use and cost with an aging Canadian population.

Methods and Results
Two systematic reviews were performed; the first compared bisphosphonates with placebo while the second compared teriparatide to bisphosphonates or placebo. Net health impact was estimated using a decision-analytic model in terms of quality-adjusted life years (QALYs). An economic evaluation compared teriparatide to bisphosphonates, or no drug therapy. The base-case for this analysis was an 80-year-old woman with at least one previous osteoporotic fracture. The budget impact of funding teriparatide and bisphosphonates in public drug plans was also assessed.

Implications for Decision Making
- Neither teriparatide nor bisphosphonates have a demonstrated direct impact on the primary prevention of clinically important fractures. None of the bisphosphonates showed reductions in hip, wrist, or other non-vertebral fractures. Alendronate’s effect is limited to an observed reduced risk of radiographic vertebral fractures in one RCT. This surrogate outcome has been linked to excess morbidity and mortality. Teriparatide’s effect could not be estimated as no primary prevention trials met the criteria for review.
- Teriparatide and some bisphosphonates have a demonstrated direct impact on the secondary prevention of clinically important fractures. Teriparatide was shown to reduce the risk of non-vertebral fractures. Alendronate and risedronate showed reductions in risks of non-vertebral fractures and of hip fractures (a major source of morbidity and mortality). Alendronate also reduced the risk of wrist fractures. Etidronate’s effect is limited to a reduced risk of vertebral fractures.
- Alendronate or no therapy are optimal. Etidronate, risedronate, and teriparatide were more costly and less effective than alendronate. Switching from etidronate to generic alendronate would cost an additional C$50 per patient every year.
- Cost effectiveness depends on age. Relative to no drug therapy, alendronate costs an additional C$169,600 per QALY for a 65-year-old woman. In a 90-year-old, alendronate therapy is less costly and more effective than no therapy.
- Publicly funding teriparatide would require an additional C$115 million in 2006. This assumes 2.5% of current bisphosphonate users would be switched to teriparatide.

This summary is based on two comprehensive health technology assessments from the Canadian Agency for Drugs and Technology in Health, Ottawa; 2006; Wells G, Cranney A, Boucher M, Peterson J, Shea B, Robinson V, Coyle D, Tugwell P. Bisphosphonates for the primary and secondary prevention of osteoporotic fractures in postmenopausal women: a meta-analysis [Technology report no 69]; and Coyle D, Tahar AH, Murphy G, Perras C, Skidmore B, Boucher M, Husereau D. Teriparatide and bisphosphonates for treatment of osteoporosis in women: a clinical and economic analysis [Technology report no 70].

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CADTH is an independent, not-for-profit organization that supports informed health care decision making by providing unbiased, reliable information about health technologies.
1 Introduction

Osteoporosis is defined as a systemic skeletal disease that is characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility, and a consequent increase in the risk of fracture. The rate of bone formation is often normal, but increased resorption\(^1\) compromises bone strength, and predisposes patients to an increased risk of fractures.\(^2\)

Osteoporosis most often affects postmenopausal women, but it also occurs in men. In Canada, approximately one in four women, and one in eight men have the disease.\(^2\) Because of the aging population, it is expected that the incidence of osteoporosis will increase significantly, and the number of hip fractures – the major source of morbidity and mortality from osteoporosis – will triple by 2040.\(^3\)

Evidence suggests that osteoporotic hip fractures may be associated with a 20% increase in mortality among older women.\(^4\) Hip fractures also threaten a person’s long-term well-being and independence. Half of women who suffer a hip fracture cannot fully recover, and depend on someone else for help with their daily activities.\(^2\)

The prevention of osteoporotic fractures would not only lower morbidity and mortality, but would also ease the financial burden associated with the disease. It is estimated that in 1993, more than C$1.3 billion was spent to provide acute care for osteoporosis patients (including hospitalization, ambulatory care, and drug therapy).\(^2\)

Most of the drugs on the market for treating osteoporosis are anti-resorptive agents, aimed at decreasing bone turnover. In Canada, the bisphosphonates etidronate, alendronate, and risedronate are the recommended first-line preventive agents in postmenopausal women with low BMD and in those with osteoporosis.\(^2\) Newer drugs, such as teriparatide, focus on increasing bone formation, and are indicated for women with severe osteoporosis who have failed other treatments.\(^8\)

Bisphosphonates are stable analogues of naturally occurring pyrophosphates. They inhibit bone loss by acting on osteoclasts – the cells associated with absorption and removal of bone. Alendronate and risedronate are taken daily or weekly; etidronate is taken in 90-day cycles to prevent osteomalacia, a complication that leads to bone softening or impaired mineralization, and increased risk of fractures. All three are taken orally.

The use of bisphosphonates in Canada grew by >200% between 1999 and 2004 (Figure 1), with the number of prescriptions increasing from 1.5 million to five million. The daily costs for bisphosphonates range from C$0.40 to C$2.00. Generic versions of alendronate recently became available in Canada.
Teriparatide (Forteo®) is a synthetic, recombinant polypeptide hormone consisting of the first 34 amino acids of human parathyroid hormone (PTH). Its anabolic effects are thought to mimic the action of endogenous PTH, to stimulate new bone formation. The continuous use of PTH may hurt the skeleton by increasing bone resorption, but used intermittently, it increases bone formation. Teriparatide is administered daily as 20 μg subcutaneous injections, for a lifetime treatment exposure of 18 months. The daily cost is C$26.50.

2 Objectives

The aim of CADTH’s first systematic review was to assess the clinical effectiveness of bisphosphonates (etidronate, alendronate, and risedronate) compared with placebo, calcium, or vitamin D, in the primary and secondary prevention of osteoporotic fractures in postmenopausal women.

The second review aimed to assess the clinical and cost effectiveness of teriparatide compared with bisphosphonates (etidronate, alendronate, and risedronate) or placebo for the primary and secondary prevention of osteoporotic fractures in postmenopausal women. This report included a budget impact analysis of funding teriparatide and bisphosphonates from the perspective of publicly funded drug plans.

3 Clinical Review

Methods

We used the Cochrane Collaboration methods for conducting systematic reviews and meta-analyses. For the review of the bisphosphonates, we searched MEDLINE®, from 1966 to November 2004, Current Contents, the Cochrane Controlled Trials Register, and EMBASE®. For the review of teriparatide, we searched MEDLINE, EMBASE, BIOSIS Previews®, and ToxFile on DIALOG® up to January 7, 2006. Parallel searches were run on PubMed and The Cochrane...
Library. No language restrictions were applied. We found grey literature by searching web sites and databases of health technology assessment and related agencies, and by hand searching the bibliographies and abstracts of selected papers and conference proceedings.

**Selection Criteria**

For the review of the bisphosphonates, randomized controlled trials (RCTs) were eligible if they compared the incidence of fractures in postmenopausal women using etidronate, alendronate, or risedronate with those using no treatment, placebo, calcium, or vitamin D. We used an algorithm to define primary versus secondary prevention according to information provided in trial reports regarding the RCT’s inclusion criteria and baseline values for BMD, previous vertebral compression fractures, and average age. For the review of teriparatide, RCTs had to examine the incidence of fractures in postmenopausal women using teriparatide compared with a bisphosphonate (alendronate, etidronate, or risedronate) or a placebo. For both reviews, we looked at RCTs of ≥1 year in duration.

We considered trials as primary prevention for both reviews if the average t-score and SD included women whose bone density was <2 SDs below the mean, or if the prevalence of vertebral fracture at baseline was <20%. Two independent reviewers abstracted information using standard data abstraction forms. Information included pertinent methodological aspects of the study design, characteristics of the participants, dose(s) of the drug, and outcomes assessed (e.g., number of vertebral, non-vertebral, hip, and wrist fractures).

**Quality Assessment**

Both systematic reviews evaluated the quality of trials. In the bisphosphonates review, this was based on the quality of allocation concealment (rated as adequate, inadequate, or unclear). This approach was favoured, because a lack of adequate allocation concealment is associated with bias. The review of teriparatide also used the Jadad quality assessment scale to assess quality; studies receiving a score of ≥3 were considered to be of higher quality.

**Data Analysis Methods**

For the review of bisphosphonates, we pooled the results to calculate the relative risk (RR) of a woman experiencing vertebral, non-vertebral, hip, and wrist fractures. This allowed us to calculate site-specific 95% confidence intervals (CIs) for the different fracture sites. We tested for association and homogeneity using chi-square test procedures. If the relative risk reduction (RRR) was significant (p<0.05), then we calculated the absolute risk reduction and the number needed to treat.

We pooled data across primary and secondary prevention trials for overall analysis, and conducted subgroup analysis for primary versus secondary fracture prevention, treatment duration, and dose. We also performed a sensitivity analysis for baseline denominators versus follow-up denominators, fixed versus random effects model, and baseline vertebral fracture rate. The latter allowed us to evaluate whether the effect of bisphosphonates on the secondary prevention of fractures varied depending on how strictly secondary prevention was defined. For the review of teriparatide, we also calculated the RR of a woman sustaining a fracture, and looked at the effect of all doses of the drug.
4 Results

A total of 30 RCTs met our inclusion criteria. The overall evidence available on fractures is more limited for teriparatide and etidronate than for alendronate and risedronate. In this Technology Overview, the RRs for bisphosphonates are based on data for the longest treatment duration and baseline denominators for the number of patients. Other analyses are available in the CADTH Technology Reports.

For etidronate, 11 trials met all selection criteria. Out of a total of 1,248 women, 624 received a placebo. Women in eight trials\textsuperscript{13-20} had established osteoporosis. These trials were classified as secondary prevention, while the remaining three\textsuperscript{21-23} were primary prevention trials.

Concealment allocation was unclear in all the trials. Seven trials\textsuperscript{13,14,16,20-23} had a loss to follow-up from 5% to 20%; for three trials,\textsuperscript{15,17,19} this was >20%, and one trial\textsuperscript{18} did not report loss to follow-up.

The pooled estimate of RR of fracture after etidronate was not statistically significant for non-vertebral, hip, or wrist fractures, whether it was used in primary or secondary prevention. For fractures of the vertebrae, the pooled RR estimate was significant for secondary prevention. When used as part of a 90-day cyclical regimen, the pooled analysis shows that etidronate reduces the RR of vertebral fractures by 47% compared with placebo. The smallest effect is a RRR of 13%, but this is clinically important, because women who sustain one incident of vertebral fracture are at risk of another the following year.\textsuperscript{24}

For alendronate, 11 trials met the selection criteria. Out of a total of 12,099 women, 5,525 received a placebo. Three trials examined primary prevention,\textsuperscript{25-27} and the remaining eight were considered to be secondary prevention trials, because they involved women with low BMD or previous fractures.\textsuperscript{28-35}

Three trials concealed allocation,\textsuperscript{26,27,29} while the others were unclear. Two trials\textsuperscript{26,28} had a loss to follow-up of <5%; five trials\textsuperscript{25,27,30,34,35} had losses to follow-up from 5% to 20%; three trials\textsuperscript{29,31,33} had losses to follow-up >20%, and one trial\textsuperscript{32} did not report losses to follow-up.

Used at a daily dose of 10 mg, alendronate was associated with a statistically significant effect in the secondary prevention of vertebral, non-vertebral, hip, and wrist fractures; and the primary prevention of vertebral fractures, compared with placebo.

For risedronate, six trials met the selection criteria. Out of a total of 13,795 women, 4,621 received a placebo. One trial was on primary prevention,\textsuperscript{36} and the other five were considered to be secondary prevention trials.\textsuperscript{37-41}

One trial concealed treatment allocation,\textsuperscript{39} while the other five were unclear. All six trials experienced losses to follow-up that were >20%, with two\textsuperscript{36,41} >40%.

Compared with placebo, the use of risedronate 5 mg daily was associated with a statistically significant reduction in the recurrence of vertebral, non-vertebral, and hip fractures, but not wrist
fractures. No fractures were observed in the one primary prevention trial, so the effect of risedronate on primary prevention could not be determined.

Adverse effects were similar among all three bisphosphonates (etidronate, alendronate, and risedronate) and placebo. In the included RCTs, none of the bisphosphonates were associated with any statistically significant difference in the rate of withdrawals due to adverse events or overall withdrawals, compared with placebo.

For teriparatide, two trials met all of the selection criteria.\textsuperscript{42,43} Out of a total of 1,783 postmenopausal women, 617 received either placebo or alendronate (control group). Both trials met the criteria for secondary prevention. In both trials, the women who were enrolled had not received treatment for osteoporosis during the past two to 24 months. Body \textit{et al.}\textsuperscript{42} included women with t-scores reflecting a SD of >2.5 below the mean for young adult women. Neer \textit{et al.}\textsuperscript{43} included women who had at least one moderate, or two mild, atraumatic vertebral fractures. In the Body \textit{et al.} trial, participants were randomized to receive high doses of teriparatide (40 μg injections daily) plus oral placebo, or 10 mg oral alendronate plus placebo injection for a median duration of 14 months. In the Neer \textit{et al.} trial, they were randomized to receive daily injections of 20 μg or 40 μg of teriparatide, or a placebo injection, for a median duration of 21 months.

Both trials were of higher quality on the five-point Jadad scale, with Body \textit{et al.} receiving a score of four, and Neer \textit{et al.}, a score of three. Allocation concealment was unclear in both. Neer \textit{et al.} did not report withdrawals, but the FDA Medical Review of this trial reported approximately 20%, with no significant differences between teriparatide and placebo groups.\textsuperscript{44} Withdrawals for any reason did not differ between teriparatide and alendronate.\textsuperscript{42}

The Neer \textit{et al.} study\textsuperscript{43} showed that, compared with placebo, teriparatide significantly reduced the risk of vertebral and non-vertebral fractures in women at high risk. No significant effect could be found for hip and wrist fractures, possibly because of small sample size. The other study\textsuperscript{42} reported no significant difference in the rate of non-vertebral fractures between teriparatide 40 μg and alendronate 10 mg.

The risk of withdrawals due to adverse events did not differ significantly between teriparatide 20 μg and placebo,\textsuperscript{43} or between teriparatide and alendronate.\textsuperscript{42} At a dose of 40 μg teriparatide, there were significantly more withdrawals due to adverse events, compared with placebo.\textsuperscript{43}

| Table 1: RR of fractures when bisphosphonates\textsuperscript{*} or teriparatide\textsuperscript{†} used for secondary prevention |
|--------------------------------------------------|----------------------------------|-----------------|-----------------|------------------|
|                     | Vertebral RR (95% CI) | Non-vertebral RR (95% CI) | Hip RR (95% CI) | Wrist RR (95% CI) |
| etidronate 400 mg   | 0.53 (0.32; 0.87)    | 1.07 (0.72; 1.60)          | 1.20 (0.37; 3.88) | 0.87 (0.32; 2.36) |
| alendronate 10 mg   | 0.55 (0.43; 0.69)    | 0.77 (0.64; 0.92)          | 0.47 (0.26; 0.85) | 0.52 (0.36; 0.75) |
| risedronate 5 mg    | 0.61 (0.50; 0.76)    | 0.80 (0.72; 0.90)          | 0.74 (0.59; 0.94) | 0.67 (0.42; 1.07) |
| teriparatide 20 μg  | 0.35 (0.22; 0.55)    | 0.65 (0.43; 0.98)          | 0.50 (0.09; 2.73) | 0.54 (0.22; 1.35) |

\textsuperscript{*}Etidronate, alendronate, and risedronate data from G. Wells \textit{et al.};\textsuperscript{45} teriparatide data based on Neer \textit{et al.};\textsuperscript{43} relative to placebo; \textsuperscript{†}statistical heterogeneity observed (p=0.069, mainly due to a study with relatively small number of subjects,\textsuperscript{3} weight=0.2% of all studies) – when random effects approach used, RR=0.52 (0.25; 1.08); RR=relative risk; CI=confidence interval.
Table 1 summarizes the effect of bisphosphonates and teriparatide on the secondary prevention of osteoporotic fractures in postmenopausal women.

5 Economic Analysis

Review of Economic Studies

The review included articles identified through an electronic search in MEDLINE, EconLit, and Current Contents between January 1990 and May 2004. This was supplemented by searching the reference list of relevant studies, and by searching the Internet. Studies were also identified from published review articles. Of the 15 studies found, 12 included at least one bisphosphonate as a comparator. The overall quality of the studies was poor, and the conclusions were inconsistent. On that basis, conclusions about the cost effectiveness of bisphosphonates in Canada were not drawn.

Primary Economic Evaluation

The cost effectiveness of teriparatide 20 µg per day was assessed using a decision analytic model in women with osteoporotic fractures at 65, 70, 80, and 90 years. Teriparatide was compared with alendronate, etidronate, risedronate, and no therapy.

The decision analytic model reflected the natural history of women with osteoporosis incorporating sequelae (e.g., fractures), and the transition between health states and residential status (e.g., admission to a long-term care facility). The health care system perspective was used for the analysis, and the time horizon was lifetime. Canadian data were used to populate the model.

Alendronate or no drug therapy was the optimal treatment option. The choice depends on a woman’s age, and the decision makers’ maximum willingness to pay for a quality-adjusted life year (QALY) gained. The older the woman, the greater the risk of fractures, suggesting a strong correlation between age and cost effectiveness. For example, alendronate is more cost effective for women ≥80 years old if the willingness to pay is >C$13,000 per QALY gained. For a 65-year-old woman, the incremental cost effectiveness ratio for alendronate compared with no therapy is C$169,600. The sensitivity analysis showed that the results were robust to changes in the parameters.

Table 2 presents the base case results for an 80-year-old woman with a previous fracture.
Table 2: Lifetime costs and QALYs associated with alternative treatment options

<table>
<thead>
<tr>
<th>80-year-old woman with previous fracture</th>
<th>Costs (C$)</th>
<th>QALYs</th>
<th>Incremental cost per QALY gained versus no therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>etidronate</td>
<td>$9,200</td>
<td>4.280</td>
<td>dominated*</td>
</tr>
<tr>
<td>no drug therapy</td>
<td>$8,700</td>
<td>4.283</td>
<td></td>
</tr>
<tr>
<td>risedronate</td>
<td>$9,200</td>
<td>4.291</td>
<td>$67,200</td>
</tr>
<tr>
<td>alendronate</td>
<td>$8,900</td>
<td>4.300</td>
<td>$13,000</td>
</tr>
<tr>
<td>teriparatide</td>
<td>$22,700</td>
<td>4.299</td>
<td>$851,000</td>
</tr>
</tbody>
</table>

*A treatment is dominated by another, if it is more costly and less effective, i.e., no matter what the willingness to pay for a health outcome, the treatment will not be cost effective. QALY=quality-adjusted life year.

Table 3 shows the optimal therapy for each age group, given our analyses of cost effectiveness.

<table>
<thead>
<tr>
<th>Table 3: Results for women with previous fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>65-year-old</td>
</tr>
<tr>
<td>70-year-old</td>
</tr>
<tr>
<td>80-year-old</td>
</tr>
<tr>
<td>90-year-old</td>
</tr>
</tbody>
</table>

\[\lambda =\text{willingness to pay.}\]

6 Limitations

While the methods used to conduct the clinical and economic reviews were robust, reviews can only be as strong as the primary studies on which they were based. Because there were limitations in the quality of the RCTs that were included, the clinical and economic reviews should be viewed with this in mind. Trial level limitations include heterogeneity in the definition of non-vertebral fracture, the lack of clarity about the concealment of treatment allocation, and sizeable losses to follow-up. Moreover, the patient population was not uniform across all studies, with some secondary prevention studies involving patients with low BMD but no proven fractures. Some etidronate trials were not necessarily designed to measure fractures, whereas for teriparatide, efficacy data were derived from only two studies, so generalizability may be limited. Information on the harm-to-benefit ratio was unavailable, making it difficult to make conclusive statements about adverse events and the long-term tolerability of teriparatide and bisphosphonates.

The economic analysis relied on various sources of Canadian data, and used an indirect comparisons approach, because no applicable comparative trials were available. In addition, both the economic analysis and the budget impact analysis were based on daily dosages for risedronate and alendronate; both drugs are available in less expensive weekly formulations that may decrease the ICER, and alter the incremental budget estimates. For the budget impact analysis, it was assumed that the bisphosphonate market was saturated, and that patients who
were prescribed teriparatide would otherwise have received a bisphosphonate; in this analysis, switch rates were modelled based on fracture incidence, because the true rate was unknown. Finally, because participants in RCTs tend to be healthier, with fewer comorbid conditions and less need to use concurrent therapies than women with osteoporosis living in the community, the ability to generalize the clinical findings of this review to the real world is reduced.

7 Health Services Impact

The potential impact of adding teriparatide to the formularies of publicly funded drug plans in Canada was explored. At an annual drug prescription cost per patient of C$9,713 (compared with C$191 to C$707 for the bisphosphonates), the impact would be substantial, even if teriparatide were used by a small portion of patients with osteoporosis. For example, if 2.5% of bisphosphonate-treated patients had switched to teriparatide in 2004, this would have cost drug plans an extra C$111 million. By 2006, if teriparatide were added as a limited benefit, governments could incur between C$115 million and C$230 million in additional drug costs, depending on utilization and the number of patients treated.

The cost effectiveness analysis found that alendronate was less costly and more effective than etidronate. Cost effectiveness depends on age. Alendronate is more cost-effective for women ≥80 years because of an increase in the baseline risk of fracture. For example, if publicly funded drug plans decided to fund alendronate instead of etidronate for women ≥65 years of age, they could incur an additional $C34 million and C$40 million in annual drug costs in 2004 and 2011 respectively, whereas the same decision for women ≥80 years of age would translate to an additional C$15 million and C$19 million in annual drug costs in 2004 and 2011 respectively.

8 Conclusion

These reports evaluated the clinical and cost effectiveness of teriparatide in relation to the three bisphosphonates available in Canada: alendronate, etidronate, and risedronate. A systematic review of the bisphosphonates and a separate systematic review for teriparatide were used to perform an economic analysis of available and effective osteoporosis drugs. These analyses show the following:

Clinical
- Compared with placebo, teriparatide 20 micrograms administered daily by subcutaneous injection confers a significant reduction in the risk of vertebral and non-vertebral fractures as secondary prevention.
- Teriparatide 40 micrograms daily and alendronate 10 mg daily are not significantly different in the secondary prevention of non-vertebral fractures.
- Teriparatide 20 micrograms daily, the recommended dose, has not been compared in head-to-head fracture trials with any bisphosphonate.
- No trials with teriparatide studied the primary prevention of osteoporotic fractures in women.
• Limited evidence supports the use of bisphosphonates in the primary prevention of osteoporotic fractures. Only alendronate has been shown to be effective in primary prevention, and this effect is limited to vertebral fractures.

• Compared with placebo, etidronate is effective in the secondary prevention of vertebral fractures.

• Compared with placebo, alendronate is effective in the secondary prevention of vertebral, non-vertebral, hip, and wrist fractures.

• Compared with placebo, risedronate is effective in the secondary prevention of vertebral, non-vertebral, and hip fractures.

Economic

• From an economic perspective, alendronate or no drug therapy is the optimal treatment option, depending on a woman’s age (i.e., alendronate is more cost effective for women ≥80 years old, because of an increase in the baseline risk of fracture) and the decision maker’s maximum willingness to pay for a QALY gained (e.g., an incremental cost effectiveness ratio of C$169,600 for alendronate versus no therapy among 65-year-old women as compared to an incremental cost effectiveness ratio of $13,000 for alendronate versus no therapy among 80-year-old women).

• Etidronate was dominated by alendronate in all age groups.

• Teriparatide is not cost effective, compared to bisphosphonates, in any scenario.

• Adding teriparatide as a limited benefit to publicly funded drug plans in Canada would result in between C$115 million to C$230 million in additional drug expenditures per year, depending on the utilization, and number of patients treated.
9 References


