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Bisphosphonates in Osteoporosis: An Analysis Focusing on Drug Claims by Seniors, 2001 to 2007

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing people to an increased risk of fracture. The disease is most common among those older than 50, with an estimated prevalence of up to one in four women and one in eight men. Since bone loss and fractures can occur without symptoms, osteoporosis may not always be recognized and consequently not treated. Bone mineral density testing is used to predict fracture risk and aids in the diagnosis of osteoporosis.

The major source of morbidity and mortality from osteoporosis is attributed to hip fractures and their complications. About 70% of hip fractures in Canada are osteoporosis related. In Canada, hip fracture hospitalizations declined by 12.7% between 2000–2001 and 2005–2006. The estimated direct costs for treating a hip fracture, both in the hospital and following discharge, average about $27,000 annually.

The annual cost of treating osteoporosis and associated fractures in Canada is estimated at $1.9 billion. These costs include hospital admissions, surgery, drug therapy, outpatient care and long-term care. Over the past decade, studies have shown a shift in osteoporosis treatments and related costs from hospital-based to community-based settings. While limited data are available on community-based costs, increases in osteoporosis drug use and costs have been reported.

A broad range of drug and non-drug interventions are used for osteoporosis prevention and treatment. The effectiveness of bisphosphonates, a drug class used for osteoporosis prevention and treatment, has been examined in several studies. A recent review found that five bisphosphonates are effective in preventing vertebral fractures: alendronate, etidronate, ibandronate, risedronate and zoledronic acid. However, only alendronate, risedronate and zoledronic acid were found to prevent hip and other non-vertebral fractures.

Patient compliance and persistence with bisphosphonate therapy have an impact on its effectiveness. Some studies have found non-compliance rates as high as 30% to 50%, leading to higher fracture risk and sub-optimal patient outcomes.
In Canada, bisphosphonate prescribing is addressed in two clinical practice guidelines: 1) those of the Society of Obstetricians and Gynecologists of Canada (SOGC) (“Canadian Consensus Conference on Osteoporosis, 2006 Update”); and 2) those of the Scientific Advisory Council for Osteoporosis Canada (“2002 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada”).21, 22 The 2006 SOGC guidelines recommend treatment with alendronate and risedronate be considered to decrease vertebral as well as hip and other non-vertebral fractures, and that etidronate be considered to decrease vertebral fractures.21

The purpose of this analysis is to look at trends in the use of etidronate, alendronate and risedronate in seniors (defined in this analysis as people 65 or older) between 2001–2002 and 2006–2007, using drug claims data from public drug programs in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia and Prince Edward Island. This analysis will look at trends in use by age and sex, use of daily and weekly formulations, and surrogate measures for compliance and persistence with therapies.

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- Jennifer Blake, MD, MSc, FRCSC, Chief of Obstetrics and Gynecology, Sunnybrook Health Sciences Centre and Women’s College Hospital; Professor and Associate Chair, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada
- Angela Juby, MBChB, LRCP (Edinburgh), LRCS (Edinburgh), LRCPS (Glasgow), Associate Professor, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
About CIHI

The Canadian Institute for Health Information (CIHI) collects and analyzes information on health and health care in Canada and makes it publicly available. Canada’s federal, provincial and territorial governments created CIHI as a not-for-profit, independent organization dedicated to forging a common approach to Canadian health information. CIHI’s goal: to provide timely, accurate and comparable information. CIHI’s data and reports inform health policies, support the effective delivery of health services and raise awareness among Canadians of the factors that contribute to good health.

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Methods

Drugs of Interest

The three bisphosphonates analyzed in the study were etidronate, alendronate and risedronate. All dosage forms and strengths of these chemicals that received Health Canada approval for osteoporosis treatment and/or prevention prior to or during the study time frame were included. Ibandronate, zoledronic acid and a new monthly formulation of risedronate were not included in the study, as they were not available in Canada during the study period (between April 2001 and March 2007). Zoledronic acid and monthly risedronate received Health Canada approval later in 2007; ibandronate was still not available in Canada as of August 2008.

Only the sequential preparation of etidronate and calcium was included in this analysis, as etidronate-only preparations are not approved for the prevention and treatment of osteoporosis in Canada. The sequential preparation is dispensed in a kit containing 14 etidronate tablets and 76 calcium tablets. During each 90-day course of therapy, a patient takes etidronate for the first 14 days and then takes calcium for the next 76 days. Any reference to etidronate for the remainder of this analysis will be referring to etidronate with calcium. It should also be noted that etidronate is counted as daily therapy in this analysis, although it is only taken for the first 14 days in a 90-day course of therapy.

The sequential preparation of etidronate and calcium was approved in Canada in 1995, and a generic version was approved in April 2008, after the end of the study period. Alendronate was approved in Canada as a daily formulation in 1996, followed by a weekly formulation in 2002. The first generic version of daily alendronate was approved in 2003, and the first generic version of weekly alendronate was approved in 2005. Risedronate was approved in Canada as a daily formulation in 2000, followed by a weekly formulation in 2002. As of August 2008, there were no generic versions of risedronate on the market in Canada.

Bisphosphonate products were identified by the drug identification numbers assigned by Health Canada, and by the World Health Organization Anatomical Therapeutic Chemical classification code M05B—Drugs Affecting Bone Structure and Mineralization.
NPDUIS Database

The drug claims data used in this analysis come from the National Prescription Drug Utilization Information System (NPDUIS) Database, as submitted by the Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia and Prince Edward Island provincial public drug programs. The NPDUIS Database houses pan-Canadian information related to public program formularies, drug claims, policies and population statistics. It was designed to provide information that supports accurate, timely and comparative analytic and reporting requirements for the establishment of sound pharmaceutical policies and the effective management of Canada’s public drug benefit programs.

The NPDUIS Database includes:

- Claims accepted by public drug programs, either for reimbursement or toward a deductible. Claims are included regardless of whether or not the patient actually used the drugs.

The NPDUIS Database does not include information regarding:

- Prescriptions that were written but never dispensed;
- Prescriptions that were dispensed but for which the associated drug costs were not submitted to, or not accepted by, the public drug programs; or
- Diagnoses or conditions for which prescriptions were written.

Calculation of Medication Possession Ratio

The medication possession ratio (MPR) can be considered a surrogate for measuring patient compliance with drug therapy, as it examines whether a patient has enough medication on hand to properly follow his or her treatment regimen. Although the MPR cannot identify if a patient is actually taking the medication as prescribed, the supply of drugs a patient has available provides insight into his or her willingness to comply with a drug therapy. Also, in the case of bisphosphonates, which have complicated dosing instructions such as a required period of fasting prior to taking the medication, even if the patient is taking the medication as often as prescribed, he or she still may not be taking the medication properly.

A high MPR is generally thought to be associated with a high rate of compliance. The optimal MPR is 100%, indicating a patient had drugs available every day of the defined treatment duration. Patients with gaps in therapy or who stop therapy will have an MPR of less than 100%. It should be noted that, although mainly considered a measure of compliance, the MPR is also affected by persistence, as gaps in therapy can lead to a lower score. Some studies have suggested that an MPR of 80% may be a reasonable threshold for persistence, as it represents fairly continuous availability of medication and fewer days without therapy.23

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i. In Manitoba, this includes accepted claims for people who are eligible for coverage under a provincial drug program but have not submitted an application and, therefore, do not have a defined deductible.
For this study, the MPR was calculated as the total quantity of a given dosage dispensed to a patient in a given year, divided by his or her treatment duration. When a patient switched between daily and weekly therapy in a given year, he or she was considered to have two courses of treatment and therefore has two MPR scores for that year. ii

The total quantity for daily therapy was calculated by summing the quantity dispensed from each bisphosphonate claim for the given dosage interval and patient in that year. iii The total quantity for patients on weekly therapy was calculated by multiplying the quantity dispensed by seven, to reflect the number of days’ worth of therapy the quantity represents. iii

To account for patients who may have started treatment partway through the year, the duration of treatment for a given year was calculated as 91 days for every quarter after and including the quarter in which the patient had his or her first claim for a given dosage interval. The only exception is where a patient switched to another dosage interval before the end of the year. As the patient was still receiving treatment, any quarters of the year following a switch in therapy were counted toward the treatment duration of the new dosage interval and not toward the treatment duration of the previous dosage interval.

Examples:

1) A patient with claims for a daily bisphosphonate in each of the first three quarters of a given year:
   • Will be considered to be receiving treatment in four quarters in that year if he or she had no claims in the final quarter.
   • Will be considered to be receiving daily therapy for three quarters and weekly therapy for one quarter if he or she had a claim for a weekly bisphosphonate in the final quarter.

2) A patient with claims for a daily bisphosphonate in the final two quarters of a given year:
   • Will be considered to be receiving daily treatment for two quarters in that year regardless of whether he or she had no bisphosphonate claims in the first two quarters or had claims for weekly bisphosphonates in either of the first two quarters.

ii. MPR scores of greater than 100% were reduced to 100%. This affected 11.8% of all patients, and reduced average MPR scores for each dosage interval by between 1.5% and 3.3% in each year.

iii. Claims with quantities of greater than one year’s supply (365 tablets for daily therapy and 52 tablets for weekly therapy) were excluded. These claims accounted for less than 0.1% of all claims.
Data Comparability

Age-Standardization
Provincial rates were age-standardized using a direct method of standardization based on the October 1, 2006, Canadian senior population. The age groups used for standardization were 65 to 74, 75 to 84 and 85 and older.iv

Drug Plan Comparison
Although public drug coverage is available to seniors (people 65 and older) in all six provinces included in the analysis, each of the drug plans is designed differently. These differences may impact drug utilization within the plans and, in turn, the claims submitted to the NPDUIS Database. One main difference is that seniors in Manitoba and Saskatchewan are covered under universal drug plans, offered to residents of all ages, whereas Alberta, New Brunswick, Nova Scotia and P.E.I. all have drug plans designed specifically for seniors. There are also other differences, such as how much a senior is required to pay for drugs through premiums, deductibles or co-payments. Seniors not covered by the publicly funded drug plan may have private drug plan coverage or pay out of pocket.

Common to all six provinces, seniors covered by provincial workers’ compensation boards or federal drug programs are not eligible for coverage under provincial drug programs. Federal drug programs include those delivered by:

- The Canadian Forces;
- The Correctional Service of Canada;
- First Nations and Inuit Health Branch;
- The Royal Canadian Mounted Police; and
- Veterans Affairs Canada.

Further information about public drug programs in Canada can be found in the NPDUIS Plan Information Document, available at www.cihi.ca/drugs.

Formulary Comparison
Differences in the coverage of drugs on provincial formularies can also lead to differences in drug utilization and are identified to provide context when conducting interprovincial comparisons. This comparison describes the formulary coverage of the three bisphosphonates as of March 31, 2007, the end of the study period.

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Formulary coverage of bisphosphonates is similar in five of the six drug programs, where etidronate is listed as a full benefit and both alendronate and risedronate are restricted benefits. The exception is P.E.I., where etidronate coverage is restricted to patients who have failed on previous therapies (such as calcium), alendronate is restricted to patients not responding to etidronate therapy and risedronate is not listed.

Among the five drug programs with similar formulary coverage for bisphosphonates, common criteria for restricted coverage relate to the presence of fractures or diagnostic criteria. The most notable difference is that only two of the five drug programs cover alendronate and risedronate for patients who do not respond to or cannot tolerate etidronate. In addition, only three of five drug programs cover alendronate and risedronate for patients with glucocorticoid-induced osteoporosis.

Without further analysis, it is unclear what effect, if any, these differences in criteria may have on bisphosphonate use across the provinces. Several other factors can influence drug utilization, such as the health of the population, prescribing patterns and the availability of non-drug therapies. Given the differences in use in provinces with similar criteria, factors other than formulary differences are likely contributing to provincial variation.

It should be noted that, from 2001 to 2007, the five provinces covering alendronate and risedronate listed them as restricted benefits with the exception of Manitoba, where these chemicals were listed as limited benefits prior to 2005. Although both limited and restricted benefits are only covered for patients who meet defined criteria, restricted benefits require that patients/prescribers seek prior approval of the drug program before making a claim, whereas limited benefits can be automatically approved at the time of claim. Manitoba’s change in formulary coverage may have been a contributing factor to the decline in its bisphosphonate use in the last two years of the study period.

**Definitions**

1. “Claimants” refers to seniors with at least one claim accepted by public drug programs, either for reimbursement or toward a deductible.

2. “Bisphosphonate users” refers to seniors with at least one claim for etidronate, alendronate or risedronate during a given year.

3. “New starts” refers to seniors with at least one claim for etidronate, alendronate or risedronate during a given year who did not have a claim for these drugs in the previous year, but had a claim for another drug in the previous year.

4. “Dosage interval” refers to the frequency a patient is expected to take the bisphosphonate medication. Daily therapy requires a patient to take one tablet a day, whereas weekly therapy requires a patient to take one a week.

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v. In Manitoba, this includes seniors with accepted claims who are eligible for coverage under a provincial drug program but have not submitted an application and, therefore, do not have a defined deductible.
5. “Stops” (also known as “discontinuations”) refers to seniors with at least one claim for etidronate, alendronate or risedronate during a given year who did not have a claim for these drugs in the following year, but had a claim for another drug in the following year.

6. “Compliance” refers to the consistency and accuracy with which a patient follows a recommended treatment regimen, usually a drug therapy regimen.25

7. “Persistence” refers to the continued and consistent use of the prescribed treatment regimen, usually a drug therapy regimen.26

Limitations
Since the NPDUIS Database does not contain information regarding diagnoses or the conditions for which prescriptions were written, it is not known whether the bisphosphonate claims were for the primary or secondary prevention of osteoporosis-related fractures or for another indication. The availability of specific strengths of alendronate and risedronate for use in osteoporosis and Paget’s disease minimized the potential impact of this. It is possible that some of the claims for the 40 mg strength of alendronate, indicated for Paget’s disease, were for weekly osteoporosis treatment prior to the availability of the 35 mg strength. However, most claims for the 40 mg strength of alendronate were assumed to be for Paget’s disease; therefore, claims for this strength were not included in the analysis.

Pan-Canadian claims-level data for bisphosphonate use in patients younger than 65 were unavailable for this study. However, using NPDUIS Database data from Saskatchewan and Manitoba, it was estimated that roughly three-quarters of bisphosphonate patients are older than 65.

Profile of Seniors With Drug Claims
In 2006–2007, there were 356,290 seniors (people 65 or older) living in Alberta, 159,986 in Manitoba, 147,268 in Saskatchewan, 106,995 in New Brunswick, 136,600 in Nova Scotia and 19,993 in P.E.I.24

The proportion of seniors who had drug claims accepted by the public drug programs in these provinces varied from 58.2% in New Brunswick to 90.8% in Manitoba (see Appendix A). The lower percentages in New Brunswick and Nova Scotia are likely related to plan design. Seniors not covered by the publicly funded drug plan may have a private drug plan or pay out of pocket. It should be noted that the total population figures include seniors who are not eligible for provincial coverage, such as those covered under federal drug plans. It should also be noted that, whereas total population figures are meant to reflect the population at a single point in time, claimant population figures reflect the number of people who made claims throughout a given year.

There is variation in the age distribution of senior claimant populations of the six provinces. Saskatchewan has the highest proportion of claimants older than 85, at 17.6%, while Alberta has the smallest proportion of claimants older than 85, at 11.7% (see Appendix A).
Analysis

Overview of Bisphosphonate Claim Trends

The following analysis examines trends in the use of etidronate, alendronate and risedronate in seniors (people 65 or older) covered by public drug programs in Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia and P.E.I. between 2001–2002 and 2006–2007. The analysis looks at trends in use by age and sex, use of daily and weekly formulations, and surrogate measures for persistence and compliance with therapy.

Expenditure

Total drug program expenditures on etidronate, alendronate and risedronate based on paid claims in five provinces\(^\text{vi}\) increased at an average annual rate of 12.7% over the study period, from more than $10.7 million in 2001–2002, to almost $19.5 million in 2006–2007. These expenditures accounted for 2.0% of total drug program expenditures in 2001–2002, and 2.2% of total drug program expenditures in 2006–2007.

Alendronate accounted for the highest proportion of drug program bisphosphonate expenditure in 2006–2007 (43.0%), followed by risedronate (38.1%) and etidronate (18.9%) (Table 1).

Table 1  Public Drug Program Expenditure on Bisphosphonates Used by Seniors in Select Provinces,* by Chemical, 2006–2007

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<thead>
<tr>
<th>Chemical</th>
<th>Drug Program Expenditure ($ Millions)</th>
<th>Percent of Drug Program Bisphosphonate Expenditure</th>
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<tr>
<td>Etidronate</td>
<td>3.7</td>
<td>18.9</td>
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<td>Alendronate</td>
<td>8.4</td>
<td>43.0</td>
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<td>Risedronate</td>
<td>7.4</td>
<td>38.1</td>
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<td>Total</td>
<td>19.5</td>
<td>100.0</td>
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Note

* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source

National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.

Utilization

The age–sex standardized rate of bisphosphonate use across the five provinces\(^\text{vi}\) increased from 8.9% in 2001–2002, to 12.9% in 2006–2007. The age–sex standardized rate of bisphosphonate use increased in each of the five provinces\(^\text{vi}\) between 2001–2002 and 2006–2007.

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\(^\text{vi}\) These figures do not include P.E.I., as data are not available prior to 2004–2005.
In Alberta, New Brunswick and Nova Scotia, the age–sex standardized rate of bisphosphonate use increased in every year, and in P.E.I. use increased in every year for which data were available (Figure 1). In Saskatchewan, the rate increased every year, with the exception of 2006–2007, when it remained relatively stable. In Manitoba, bisphosphonate use declined in the last two years of the study period. This decline followed a change to the formulary listing of alendronate and risedronate in 2005.vii

In 2001–2002, the age–sex standardized rate of bisphosphonate use among seniors varied from 5.2% in Manitoba to 13.4% in Alberta. In 2006–2007, the rate varied from 1.7% in P.E.I. to 7.5% in Manitoba to 18.0% in Alberta. Prince Edward Island will be excluded from all aggregate analyses (that is, analyses not at the provincial level), as their data were not available prior to 2004–2005.

**Figure 1** Age–Sex Standardized Percentage Rate of Bisphosphonate Use Among Seniors on Public Drug Programs in Select Provinces,* by Province, 2001–2002 to 2006–2007

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<td>2001–2002</td>
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<td>2006–2007</td>
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* The six provinces submitting claims data to the NPDUIS Database as of November 2008.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.

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vii. For more detail, see the Formulary Comparison section of this Analysis in Brief.
Bisphosphonate Claim Trends: Age and Sex

The use of bisphosphonates was highest among females and older seniors (Figure 2). In 2006–2007, the rate of bisphosphonate use among female seniors was 20.4%, more than six times the rate of use among male claimants (3.3%). The higher prevalence of osteoporosis in senior women is a contributing factor to their higher use of bisphosphonates. The under-treatment and under-diagnosis of osteoporosis in men have been reported in the literature and may also be factors in their lower use.26–28

The lowest rate of bisphosphonate use among both male and female seniors was found in those between 65 and 74. Among male seniors, the highest rate of bisphosphonate use was found in those 85 and older (5.0%), whereas among female seniors, those between 75 and 84 had the highest rate of use (23.1%). This may be due, in part, to the fact that osteoporosis is often unrecognized in men until the condition is at an advanced stage.27

Figure 2  Percentage Rate of Bisphosphonate Use Among Seniors on Public Drug Programs in Select Provinces, * by Age Group and Sex, 2006–2007

![Percentage Rate of Bisphosphonate Use Among Seniors](image)

Note
* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
Bisphosphonate Claim Trends: By Chemical

Etidronate use declined at an average annual rate of 5.0% during the study period. Despite this, it had the highest rate of use among the three bisphosphonates until surpassed by alendronate in 2005–2006 (Figure 3). Alendronate and risedronate, the two newer products, both experienced high growth rates, at 23.2% and 43.0% per year, respectively. In 2006–2007, alendronate had the highest rate of use among senior claimants, at 5.9%, followed by etidronate at 4.9% and risedronate at 2.9%.

The changes in rates of use appear to be due, in part, to patients switching from etidronate to one of the two newer bisphosphonates. Of etidronate users in 2001–2002 who were still bisphosphonate users in 2006–2007, 17.4% were using risedronate and 31.4% were using alendronate. These numbers exclude users with claims for multiple bisphosphonates in either year (4.8% of users in 2001–2002, 3.6% in 2006–2007). In both cases, more than 95% of etidronate users who switched to either alendronate or risedronate switched to a weekly formulation. Several factors may have contributed to this trend, including a preference for weekly therapy (not available for etidronate) or a preference for a bisphosphonate effective in reducing the risk of both vertebral and non-vertebral fractures.14

Switching from alendronate and risedronate also occurred, though at a lesser rate. Of alendronate users in 2001–2002 who were still bisphosphonate users in 2006–2007, 8.5% switched to risedronate, while only 1.2% switched to etidronate. Of risedronate users in 2001–2002 who were still bisphosphonate users in 2006–2007, 18.0% were using alendronate, while only 2.2% were using etidronate. Again, these numbers exclude users with claims for multiple bisphosphonates in either year. Factors that may have contributed to these switches include side effects or lack of efficacy.
**Bisphosphonate Claim Trends: New Starts**

A patient was defined as having started bisphosphonate therapy in a given year if he or she had at least one bisphosphonate claim in that year but not in the previous year, and had claims for drugs other than bisphosphonates in the previous year.

The rate of new bisphosphonate starts among senior claimants showed a slight decline in all provinces during the study period (Figure 4). In 2002–2003, 2.3% of senior claimants started bisphosphonate therapy; this rate dropped to 1.9% in 2006–2007. The rate declined in almost every year, with the exception of 2003–2004, when there was an increase in new starts in four of the five provinces. This followed the release of the “2002 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada” and the introduction of weekly therapy, which also occurred in 2002.
In 2002–2003, 63.3% of new bisphosphonate users were started on etidronate, 28.1% on alendronate and 8.6% on risedronate. While the percentage of new bisphosphonate users started on either alendronate or risedronate increased (Figure 5) and the percentage of those started on etidronate declined, in 2006–2007, etidronate was still the most common first-line bisphosphonate therapy, accounting for 44.9% of new bisphosphonate users. Alendronate starts were the next highest, at 34.4%, followed by risedronate starts, at 20.6%. The less restrictive formulary listing of etidronate in most of the drug programs may have contributed to its continued use as a first-line bisphosphonate therapy.
**Bisphosphonate Claim Trends: By Dosage Interval**

Weekly therapy was introduced in Canada in 2002, near the beginning of the study period. Given this, in 2001–2002, almost all bisphosphonate users (9.3% of senior claimants) were on daily therapy, while only a small proportion (less than 0.1% of senior claimants) were on weekly therapy (Figure 6). By 2006–2007, there was a significant shift to the use of weekly therapy, with 8.4% of senior claimants on weekly bisphosphonate therapy, compared with 5.3% on daily therapy. Of senior claimants on daily therapy in 2006–2007, 93.9% were on etidronate, while only 6.3% were on alendronate or risedronate (a small percentage had claims for more than one chemical). As previously noted, etidronate is considered a daily therapy in this analysis, although it is only taken for the first 14 days of a 90-day course of therapy (calcium is taken daily for the remaining 76 days).

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**Note**

* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

**Source**

National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
The shift from daily to weekly therapy seems to be due in large part to switching between therapies. Of daily bisphosphonate users in 2001–2002 who were still taking bisphosphonates in 2006–2007, 59.7% were on weekly bisphosphonate therapy in 2006–2007. This number excludes users with claims for both therapies in either year (less than 0.1% of users in 2001–2002, 3.3% in 2006–2007). Switching may be due in part to a preference for a weekly therapy or for a bisphosphonate that reduces the risk of both vertebral and non-vertebral fractures.

Figure 6  Percentage Rate of Bisphosphonate Use Among Seniors on Public Drug Programs in Select Provinces, * by Dosage Interval, 2001–2002 to 2006–2007

![Diagram showing percentage rate of bisphosphonate use among seniors on public drug programs in select provinces, by dosage interval, 2001–2002 to 2006–2007.](image)

Note
* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.

New starts also contributed to the shift from daily to weekly therapy. As with switching, trends were impacted by changes in the availability of daily and weekly formulations.

In 2002–2003, the majority (89.1%) of new starts were on daily therapy, as weekly therapy was only made available in early 2002 (Figure 7). However, by 2003–2004, the majority of new starts were given weekly therapy. This trend remained relatively stable until 2006–2007, when 54.2% of new starts were on weekly therapy and 45.8% were on daily therapy. Almost all new daily starts were with etidronate.
Figure 7  Percentage Rate of Bisphosphonate Use Among New Bisphosphonate Starts on Public Drug Programs in Select Provinces, * by Dosage Interval, 2002–2003 to 2006–2007

Note
* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.

Persistence and Compliance With Bisphosphonate Therapy

Several studies have reported sub-optimal levels of persistence and compliance with bisphosphonate therapy. The impacts reported in these studies include reduced clinical benefit and poor outcomes, including a higher risk of fracture. Two of the factors implicated with non-compliance are the inconvenience and complexity of dosing regimens (for example, a required period of fasting prior to taking the medication). Studies have shown that, although compliance may improve with weekly regimens compared to daily regimens, compliance with weekly therapy remains sub-optimal.

Two surrogate measures for persistence and compliance with bisphosphonate therapy were examined in this study. Stops of bisphosphonate therapy were used as a measure of persistence with therapy, and the medication possession ratio was used as a measure of compliance with therapy. While these measures provide some insight as to whether patients take their medications as prescribed, they do not provide a complete picture of patient persistence and compliance. Even if a patient is taking his or her bisphosphonate as often as prescribed, and getting regular refills, its efficacy may be limited if he or she is not taking the medication properly.
Bisphosphonate Stops

A patient was defined as having stopped bisphosphonate therapy in a given year if he or she had at least one bisphosphonate claim in that year but not in the following year, and had claims for drugs other than bisphosphonates in the following year. As stops do not examine gaps in therapy, they only present a partial picture of persistence.

The overall discontinuation rate among senior bisphosphonate users declined from 15.5% in 2001–2002, to 12.0% in 2005–2006. Seniors on daily bisphosphonate therapy stopped their treatment more often than seniors on weekly therapy (Figure 8). In 2005–2006, 14.2% of daily users discontinued bisphosphonate therapy, whereas only 10.5% of weekly users stopped therapy.

The decrease in stops among daily users and increase in stops among weekly users between 2001–2002 and 2004–2005 may be due in part to daily users, who previously would have simply stopped bisphosphonate therapy, being switched to weekly therapy before stopping. In 2004–2005, 45.5% of patients who stopped weekly therapy had previous claims for daily bisphosphonate therapy.

Figure 8  Stops, as a Percentage of Senior Bisphosphonate Users on Public Drug Programs in Select Provinces, * by Dosage Interval, 2001–2002 to 2005–2006

Note
* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
Stop rates among users of each of the three chemicals declined slightly over the study period. Etidronate users discontinued bisphosphonate treatment at a greater rate than alendronate and risedronate users (Figure 9). In 2005–2006, 14.4% of etidronate users stopped their therapy, whereas only 10.8% of alendronate users and 10.1% of risedronate users discontinued therapy. Several factors may have contributed to discontinuation of a specific bisphosphonate, including lack of efficacy, side effects or the inconvenience of the dosing regimen.

Figure 9  Stops, as a Percentage of Senior Bisphosphonate Users on Public Drug Programs in Select Provinces,* by Chemical, 2001–2002 to 2005–2006

Note
* Five provinces submitting claims data to the NPDUIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.

Medication Possession Ratio
The medication possession ratio (MPR) can be considered a surrogate for measuring patient compliance with drug therapy. The MPR focuses on the number of days a medication was available to a patient for use in relation to a defined treatment duration. Although the MPR cannot identify if a patient is actually taking the medication as prescribed, the supply of drug a patient has available provides insight into his or her willingness to comply with a drug therapy.
For this study, the MPR was calculated as the total quantity of a given dosage dispensed to a patient in a given year, divided by the treatment duration (see Methods section for detailed calculation). Daily and weekly bisphosphonate users had similar MPR scores in each year, except for the first year in which weekly therapy was introduced (Figure 10). There was little change in the MPR among either daily or weekly users during the study period. In 2006–2007, patients on daily bisphosphonate regimens had drugs available for 82.7% of their treatment duration, compared with patients on weekly regimens, who had drugs available for 82.1% of their treatment duration.

As noted earlier, the MPR is also affected by gaps in therapy, and a score of 80% may be a reasonable threshold to indicate persistence. In 2006–2007, 69.3% of weekly patients had an MPR of 80% or higher, compared with 64.5% of daily patients.

Figure 10 Medication Possession Ratio Among Seniors on Public Drug Programs in Select Provinces, * by Dosage Interval, 2001–2002 to 2006–2007

Note
* Five provinces submitting claims data to the NPDIS Database as of November 2008: Alberta, Saskatchewan, Manitoba, New Brunswick and Nova Scotia.

Source
National Prescription Drug Utilization Information System Database, Canadian Institute for Health Information.
Conclusion

In Canada, osteoporosis affects up to one in four women older than 50 and up to one in eight men older than 50.² Bisphosphonates are effective in reducing the risk of fractures and are used to prevent and treat osteoporosis.¹¹, ¹⁴–¹⁷

This analysis of NPDUIS Database data from Alberta, Saskatchewan, Manitoba, New Brunswick, Nova Scotia and P.E.I. examines trends in the use of etidronate, alendronate and risedronate in seniors between 2001–2002 and 2006–2007. Current Canadian guidelines recommend the use of alendronate and risedronate to decrease vertebral, as well as hip and other non-vertebral, fractures and the use of etidronate to decrease vertebral fractures.²¹, ²²

During the study period, drug program expenditures on the three bisphosphonates increased at an average annual rate of 12.7%, accounting for 2.2% of total expenditures in 2006–2007. The age–sex standardized rate of bisphosphonate use across all provinces increased from 8.9% in 2001–2002, to 12.9% in 2006–2007. Use was highest among females and seniors older than 75. The use of etidronate, the first bisphosphonate marketed in Canada, declined at an average annual rate of 5.0% during the study period, while the use of alendronate and risedronate increased at an average annual rate of 23.2% and 43.0%, respectively. In 2006–2007, alendronate had the highest rate of use, at 5.9%, followed by etidronate at 4.9% and risedronate at 2.9%.

Although the percentage of new bisphosphonate users starting on either alendronate or risedronate increased and the percentage of those starting on etidronate declined during the study period, in 2006–2007, etidronate was still the most common first-line bisphosphonate therapy, accounting for 44.9% of new bisphosphonate users. Alendronate starts were the next highest, at 34.4%, followed by risedronate starts at 20.6%.

There was a significant shift from the use of daily to weekly therapies, with 59.7% of daily bisphosphonate users in 2001–2002 switching to weekly bisphosphonate therapy in 2006–2007. New starts on bisphosphonate therapy exhibited a similar pattern of preference for weekly therapy, with 54.2% of new users starting with a weekly bisphosphonate. These trends may be related to efforts to improve persistence and compliance with therapy. However, an examination of surrogate measures for persistence and compliance with therapy showed little difference between daily and weekly users.

Further analysis is needed to understand the full impact of the use of bisphosphonates on hip fractures and consequential hospitalization. It will also be important to monitor the use and impact of new bisphosphonates as well as other drug therapies used in the treatment and prevention of osteoporosis.
Appendix A: Distribution of Total Senior Population and Senior Claimants on Public Drug Programs in Select Provinces, by Age and Sex, 2006–2007

### Alberta

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 356,290)</th>
<th>Senior Claimants (n = 318,521)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>44.8%</td>
<td>44.1%</td>
</tr>
<tr>
<td>Female</td>
<td>55.2%</td>
<td>55.9%</td>
</tr>
<tr>
<td>65–74</td>
<td>53.5%</td>
<td>52.8%</td>
</tr>
<tr>
<td>75–84</td>
<td>34.4%</td>
<td>35.5%</td>
</tr>
<tr>
<td>85+</td>
<td>12.1%</td>
<td>11.7%</td>
</tr>
</tbody>
</table>

### Saskatchewan

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 147,268)</th>
<th>Senior Claimants (n = 132,530)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43.5%</td>
<td>41.8%</td>
</tr>
<tr>
<td>Female</td>
<td>56.5%</td>
<td>58.2%</td>
</tr>
<tr>
<td>65–74</td>
<td>47.1%</td>
<td>45.1%</td>
</tr>
<tr>
<td>75–84</td>
<td>36.6%</td>
<td>37.3%</td>
</tr>
<tr>
<td>85+</td>
<td>16.3%</td>
<td>17.6%</td>
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</table>

### Manitoba

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 159,986)</th>
<th>Senior Claimants (n = 145,263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>42.8%</td>
<td>41.6%</td>
</tr>
<tr>
<td>Female</td>
<td>57.2%</td>
<td>58.4%</td>
</tr>
<tr>
<td>65–74</td>
<td>48.6%</td>
<td>46.9%</td>
</tr>
<tr>
<td>75–84</td>
<td>36.4%</td>
<td>37.0%</td>
</tr>
<tr>
<td>85+</td>
<td>15.0%</td>
<td>16.1%</td>
</tr>
</tbody>
</table>

viii. The six provinces submitting claims data to the NPUIIS Database as of November 2008.
New Brunswick

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 106,995)</th>
<th>Senior Claimants (n = 62,267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43.0%</td>
<td>37.6%</td>
</tr>
<tr>
<td>Female</td>
<td>57.0%</td>
<td>62.4%</td>
</tr>
<tr>
<td>65–74</td>
<td>52.4%</td>
<td>46.7%</td>
</tr>
<tr>
<td>75–84</td>
<td>34.3%</td>
<td>36.2%</td>
</tr>
<tr>
<td>85+</td>
<td>13.3%</td>
<td>17.1%</td>
</tr>
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Nova Scotia

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 136,600)</th>
<th>Senior Claimants (n = 94,730)</th>
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<tbody>
<tr>
<td>Male</td>
<td>43.4%</td>
<td>37.9%</td>
</tr>
<tr>
<td>Female</td>
<td>56.6%</td>
<td>62.1%</td>
</tr>
<tr>
<td>65–74</td>
<td>53.0%</td>
<td>48.5%</td>
</tr>
<tr>
<td>75–84</td>
<td>33.3%</td>
<td>35.1%</td>
</tr>
<tr>
<td>85+</td>
<td>13.7%</td>
<td>16.4%</td>
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</tbody>
</table>

Prince Edward Island

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 19,993)</th>
<th>Senior Claimants (n = 16,256)</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>43.2%</td>
<td>41.0%</td>
</tr>
<tr>
<td>Female</td>
<td>56.8%</td>
<td>59.0%</td>
</tr>
<tr>
<td>65–74</td>
<td>53.5%</td>
<td>51.3%</td>
</tr>
<tr>
<td>75–84</td>
<td>32.8%</td>
<td>34.9%</td>
</tr>
<tr>
<td>85+</td>
<td>13.6%</td>
<td>13.8%</td>
</tr>
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</table>

Canada: Standard Population

<table>
<thead>
<tr>
<th>Group</th>
<th>Senior Population (n = 4,340,661)</th>
<th>Senior Claimants (N/A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43.7%</td>
<td>N/A</td>
</tr>
<tr>
<td>Female</td>
<td>56.3%</td>
<td>N/A</td>
</tr>
<tr>
<td>65–74</td>
<td>52.6%</td>
<td>N/A</td>
</tr>
<tr>
<td>75–84</td>
<td>35.2%</td>
<td>N/A</td>
</tr>
<tr>
<td>85+</td>
<td>12.2%</td>
<td>N/A</td>
</tr>
</tbody>
</table>
References


14. Agency for Healthcare Research and Quality, *Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis. AHRQ Publication No. 08-EHC008-EF* (Rockville, Maryland: AHRQ, 2007).


