

# Adherence with Oral Bisphosphonate Therapy for Osteoporosis Among Patients in Canadian Clinical Practice

Nader Habib, MD  
Heather McDonald-Blumer, MD  
Michele Moss, MBChB, MCFP  
Angèle Turcotte, MD

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Osteoporosis is a significant problem in Canada and elsewhere.<sup>1</sup> As the population is aging, fragility fractures caused by osteoporosis are contributing to increasing healthcare costs.<sup>2</sup> Although treatment with therapies such as oral bisphosphonates has been shown to prevent fractures in clinical trials, adherence to therapy for osteoporosis—as for other chronic, asymptomatic diseases—is often poor in a clinical practice setting.<sup>1</sup> Nonadherence to therapy in turn is linked with reduced drug effectiveness, increased rate of fractures and hospitalization, and increased medical costs.<sup>1</sup>

It is estimated that almost two million Canadians have osteoporosis, and among those older than 50, one in four women and at least one in eight men have osteoporosis.<sup>3</sup> A large, population-based survey of Ontario residents aged 55 years and older found that 15% of the women and 5% of the men had suffered an osteoporotic fracture.<sup>4</sup> Similarly, a large, retrospective cohort study of women aged 50 years and older living in Manitoba reported that, during a 3.2-year period following baseline bone density testing, 4.6% of the women experienced an osteoporotic fracture.<sup>5</sup>

Osteoporotic fractures and related hospitalization has a large impact on healthcare costs. A study estimated that, in 1995/1996, annual healthcare costs associated with hip fractures in Canada were \$650 million, and by

2041 these costs were projected to increase to \$2.4 billion.<sup>2</sup> Osteoporosis Canada estimates that the current cost of treating osteoporosis and fractures related to this disease is \$1.9 billion a year.<sup>3</sup>

Pharmacotherapy can play an important role in reducing risk of fractures, but the benefits depend on adherence to treatment. According to the recently updated Canadian Clinical Practice Guidelines for Osteoporosis, there is evidence that pharmacotherapy reduces the risk of vertebral fracture by 30% to 70%, depending on the agent and the level of the patient's adherence to treatment, and that some interventions prevent nonvertebral and/or hip fractures.<sup>6</sup> One study showed that persistence with bisphosphonate therapy was linked with up to a 60% lower risk of hip fracture.<sup>1</sup> Another study determined patients with refill compliance of at least 80% for oral bisphosphonates were significantly less likely to experience a fracture than those with lower rates of refill compliance.<sup>7</sup>

The current osteoporosis assessment program looks at adherence (compliance and persistence) to the three oral bisphosphonates that are available in Canada—alendronate, risedronate, and etidronate. According to Canadian guidelines, alendronate and risedronate are among the recommended first-line therapies to prevent osteoporosis-related fractures in post-menopausal women and

in men, and etidronate is a recommended second-line therapy for menopausal women who are intolerant to first-line therapies.

The assessment program aimed to identify common gaps in the management of patients with osteoporosis who were treated with oral bisphosphonates through an online survey of Canadian physicians.

Adherence in the study was defined as encompassing both compliance and persistence: compliance being defined as taking the medication as prescribed and not missing doses, while persistence was defined as continuing the treatment for the prescribed duration.

### *Methods*

Canadian family physicians were invited to participate in an online survey about osteoporosis management. The physicians were required to provide information about 15 consecutive patients who had been treated with oral

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bisphosphonates for three months to at least five years and were free from comorbid disease that would have required stopping treatment.

The physicians who participated in the assessment program answered an online questionnaire, which collected information about their practice profile, including practice type and location (e.g., solo, clinic, urban), number

of years in practice, patient type (age range and gender), number of patients with osteoporosis seen in a week, and osteoporosis patient management actions. Participating physicians were also asked to indicate their agreement with a series of 26 statements assessing general osteoporosis management.

For each patient, physicians also filled in a patient profile that provided the name and dosage of the patient's current bisphosphonate therapy, the patient's replies to 10 questions, and relevant data from the patient's chart. In the patient interview, patients were asked when they took the bisphosphonate, what liquid or food they took it with, whether they took it with other medications or with calcium, the number of doses they missed in the past three months, and the reasons for missing these doses. Data from the patient's chart that was entered into the questionnaire included age, gender, and dates of first bisphosphonate prescription and of any fracture. No identifying data, such as the patient's name, postal code or birthdate was collected, and all information is presented as aggregate to ensure confidentiality is maintained.

Physicians were also asked whether they would modify the patient's osteoporosis management plan based on interview and chart information.

### *Results*

The 159 physicians who participated in the survey were mainly from Quebec (49%) and Ontario (31%), but also from Alberta (7%) and British Columbia (13%). Most (74%) had been in practice over 20 years and more than half (59%) were in group practice. Most physicians (87%) worked in a private office or clinic, although 18% worked in a hospital and 9% worked in a nursing home, and most (85%) practiced in an urban or suburban area.

Patient profiles were obtained from 1,947 patients who were currently taking oral bisphosphonates. Most study patients were elderly with a mean age 70 years, and 86% were female.

On average, 61% of the patients in the participants' practices were female and about half were aged 50 and older. On average, each week, over 40% of the physicians saw about 11 to 15 patients with osteoporosis.

TABLE 1.

## Physician Perceptions of Osteoporosis-management Actions

Osteoporosis-management action*	Percentage of physicians who indicated that they regularly perform this action (N = 159)
I counsel patients about appropriate lifestyle modifications.	99
I assess adherence to calcium and vitamin D supplementation.	98
I ask about side effects.	95
I assess adherence to medication.	93
I ask postmenopausal women about fragility fractures.	92
I ask about concomitant medications prior to making treatment decisions.	91
I discuss patient preferences before making treatment decisions.	89
I automatically measure BMD for women aged 65 years and over.	85
I assess risk of non-adherence before making treatment decisions.	78
I ask men over the age of 50 years about fragility fractures.	40
I automatically measure BMD for men aged 65 years and over.	32

\*The actions are some of the statements that physicians could select to describe their strategies for treating patients with osteoporosis.

Almost all physicians (93%) claimed that they regularly assessed adherence to osteoporosis medication, although fewer physicians (78%) claimed that they assessed this risk before making treatment decisions (Table 1). While the majority of physicians claimed they regularly asked postmenopausal women about fragility fractures and automatically measured BMD for women aged 65 years and over, less than half of physicians indicated they asked men over the age of 50 years about fragility fractures or automatically measured BMD for men aged 65 years and over (Table 1).

The bisphosphonate types and dosages taken by the patients are summarized in Table 2. Just over half of the patients (55%) were taking risedronate, and less than half (40%) were taking alendronate, while the remainder (5%) were taking etidronate. Most patients (82%) were on a weekly dosing regimen, while a few (12%) received monthly dosing of risedronate, and very few (1%) re-

ceived daily dosing of either drug. The etidronate dosing regimen consisted of taking the drug for 14 days and then taking calcium for 10 days.

About half of the patients had been receiving oral bisphosphonate therapy for two to five years, although about one third of the patients had been on it for longer than that, 6% of patients had been on this treatment for less than a year.

About 1 in 6 patients reported experiencing adverse effects from bisphosphonates. In these patients, adverse effects were mainly occasional (52% of patients) or rare (21%), although some patients (27%) had adverse effects with every dose.

### Adherence Results

Only 79% of patients taking risedronate or alendronate were taking the drug at the correct time—first thing in the morning, at least half an hour before eating (Table 3).

TABLE 2.

## Type and Dosage of Oral Bisphosphonate

Drug	Dosage type	Number of patients (n [%]) (N = 1,947)
Alendronate (branded)	10 mg/day	3 (0.2%)
	70 mg/week	261 (13.4%)
Alendronate (generic)	5 mg/day	3 (0.2%)
	10 mg/day	5 (0.3%)
	70 mg/week	317 (16.3%)
Alendronate/cholecalciferol	70 mg/2800 IU/week	47 (2.4%)
	70 mg/5600 IU/week	150 (7.7%)
Etidronate	400 mg/day for 14 days, then calcium for 10 days	97 (5.0%)
Risedronate	5 mg/day	11 (0.6%)
	35mg/week	820 (42.1%)
	150 mg/month	233 (12.0%)

Note: percentages may not add to 100% due to rounding.

Even fewer patients taking etidronate were taking it at the correct time—mid morning, mid afternoon or evening, at least 2 hours before and after eating (defined in this analysis as “nighttime” or “other”). Incorrect dos-

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ing times that patients took their bisphosphonate included just before breakfast (13%), when still in bed (4%), with breakfast (2%), or when they remembered (1%).

About 16% of patients were not taking their bisphosphonate correctly with a glass of water, but were instead

taking it with a sip of water, another liquid, or food. A similar number of patients were incorrectly taking the drug with calcium or with other medications.

Over half of the patients (57%) reported missing doses in the past 3 months, due to forgetfulness (51%), side effects (9%), or other unspecified reasons (40%). However, overall persistence (one of the 2 components of adherence) appeared to be high, with patients having missed an average of 7.6% of doses in the past 3 months. Table 4 summarizes the percent of missed doses by patient type.

Patients were deemed to be non-compliant (the other component of adherence) if they had missed 80% or more doses in the past 3 months, took bisphosphonate with something other than a glass of water, and/or did not take the bisphosphonate at the correct time. Based on these criteria, 49% of patients were considered to be non-compliant.

In contrast, physicians reported that compliance was poor for only 12% of patients and persistence was poor for 3% of patients. The physicians indicated that, as a re-

TABLE 3.

## Percent of Patients Taking Bisphosphonate at the Correct Time

Drug	Time of day drug should be taken	Percentage of patients taking the drug at the correct time (N = 1,947)
Alendronate (40% of patients)	First thing in the morning, at least half an hour before eating (defined in this analysis as "> 30 minutes before breakfast")	79
Risedronate (55% of patients)	First thing in the morning, at least half an hour before eating (defined in this analysis as "> 30 minutes before breakfast")	78
Etidronate (5% of patients)	Mid morning, mid afternoon or evening, at least 2 hours before and after eating (defined in this analysis as "nighttime" or "other")	19

sult, they would provide counselling on the importance of taking medication and supplements to 36% of patients.

### Discussion

This online survey of Canadian clinicians found a striking discrepancy between the compliance with oral bisphosphonate therapy that was reported by physicians and by patients. Even though over 90% of physicians claimed to be regularly assessing patient adherence to oral bisphosphonates, nearly half (49%) of the patients were not compliant with therapy, since they took the drug in the wrong way, at the wrong time, or missed doses.

This lack of compliance is similar to that reported in a recent large, observational, American study, which used data from insurance claims databases to investigate bisphosphonate compliance in over 35,000 women aged 45 years and older with a diagnosis of postmenopausal osteoporosis. Only 43% of women in this study were considered compliant over the two-year study period based on the objective measure of medication possession ratio (MPR; the number of pills dispensed divided by time).<sup>7</sup> Similarly, in a French study based on physician and patient replies to a questionnaire about osteoporosis treatment, only two thirds of the patients rated themselves as fully compliant though physi-

cians thought compliance was adequate for over 95% of their patients.<sup>8</sup>

Limitations of this assessment program include its observational nature, and the facts that it relied on self-reported compliance rather than objective measures

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such as pill counting and that it was not designed to gather detailed information about why patients may have skipped doses. Patients were asked if the main

**TABLE 4.**  
**Percent of Missed Doses of Oral Bisphosphonate**

Patient population	Percentage of missed doses of bisphosphonate* (Mean [SD])
<b>Dosage regimen</b>	
Daily (n = 22)	2.1 (3.8)
Weekly (n = 1595)	8.0 (16.8)
Monthly (n = 233)	5.2 (17.9)
14 Days in 3 Months (n = 97)	16.3 (24.1)
<b>Overall (n = 1,947)</b>	<b>7.6 (17.0)</b>
<b>Medication-taking practices</b>	
Taken at correct time (n = 1,408)	6.2 (15.1)
Taken at incorrect time (n = 462)	11.6 (20.7)
Taken with a glass of water (n = 1,636)	6.5 (15.4)
Taken with food, other liquid, sip of water, or nothing (n = 311)	13.5 (23.8)
Taken with calcium (n = 365)	10.9 (18.9)
Taken with other medication (n=289)	11.1 (19.4)
<b>Fracture since starting bisphosphonate</b>	
Yes (n = 186)	10.0 (18.5)
No (n = 1,761)	7.4 (16.8)

\* in the last 3 months

reason for missing doses was “forgetfulness,” “side effects,” or “other.” It is possible that the “other” reasons for missing a dose (cited by 42% of patients who missed doses) included the challenge of meeting the strict dosing regimen with bisphosphonates, or not understanding the importance of taking the medication. These reasons for suboptimal compliance with bisphosphonates were identified in a recent Canadian study that was based on focus groups with 37 postmenopausal women who were taking therapies for osteoporosis. That study suggested that healthcare providers’ willingness to spend time explaining medications and providing regular follow-up might motivate patients to continue taking their medication.<sup>9</sup> A recent review of other studies identified multiple reasons for non-compliance with bisphosphonate therapy.<sup>1</sup> Cost did not appear to play a large role, and the most common reasons given for non-compliance in past

studies were side effects (which were cited as a reason for missing doses by 8% of patients who missed doses in the current assessment program) and perceptions about effectiveness and safety.<sup>1</sup>

The current assessment program did not distinguish between compliance in patients who were newly prescribed bisphosphonates versus compliance in patients who were taking these drugs for a longer time. Another study found that more than 50% of women taking either daily or weekly bisphosphonates had discontinued at 1 year.<sup>1</sup> The assessment program was also not powered to assess reinitiation rates among patients who discontinued bisphosphonate therapy and then resumed taking it, which have been estimated to be as high as 30% within 6 months and 50% within 2 years.<sup>1</sup>


Although identifying new ways to improve adherence to osteoporosis therapy was also beyond the scope of this survey, four recent randomized trials reported

various strategies. Simply providing the patient with leaflets did not appear to improve adherence. Strategies that involved physician-patient interaction appeared to be more effective. For example, persistence was improved in patients with whom bone mineral density (BMD) test results were discussed. Some patients indicated they would like to receive email reminders about the importance of taking their bisphosphonate therapy.<sup>1</sup>

Men comprised 14% of this sample, which is consistent with the estimate that about 1 in 8 men in Canada have osteoporosis. Although gender differences in diagnosing and treating this disease is beyond the scope of this assessment program, it is important for physicians to be aware that men are sometimes forgotten when it comes to screening for osteoporosis.<sup>10</sup> Based on the authors' clinical experience, and on discussions in the Canadian family-physician community, it appears that only about one third of men who require a BMD test are being offered one, and only 14% of men are being asked about fragility fractures. In addition, although detecting a decrease in height is an effective, inexpensive way to detect vertebral fractures, it appears that less than two thirds of elderly Canadians have their height measured annually.<sup>11</sup>

To summarize, this program identifies a gap in physician- and patient-perceived compliance among patients who are receiving oral bisphosphonates in Canadian

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clinical practice. It draws attention to an ongoing need for physicians to determine and improve patient compliance, and thereby adherence, with oral bisphosphonate therapy to reduce fracture risk. 

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