Determinants of Persistence with Weekly Bisphosphonates in Patients with Osteoporosis

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ABSTRACT. ***Objective.*** To evaluate the relationship between the persistent acquisition of bisphosphonate (BP) osteoporosis (OP) medication and the following factors: BP prescribed; whether BP was first used to replace another non-BP drug for OP; patient age; type of drug coverage; specialty of initial prescribing physician; and number and type of comorbid diseases.

Methods. Data were acquired from a large Canadian public and private claims database, which included information on all prescriptions filled, including drug preparation, dose, dosing schedule, number of tablets dispensed, and the date of dispensing. A total of 62,897 female patients who had initiated weekly BP therapy (risedronate 35 mg once weekly or alendronate 70 mg once weekly) for OP between January 1, 2003, and February 28, 2006 were analyzed, each for 12 months. Persistence rates were determined for 6 and 12 months post initial prescription. Regression models were used to assess the influence of various patient, physician, and drug factors.

Results. Persistence of BP declined over the first year of BP prescription, to between 60% and 74% by 6 months, and between 37% and 59% by 12 months, depending upon a variety of factors. The factors that most adversely influenced BP persistence were patient age (< 65 vs ≥ 65; $p < 0.0001$); the type of drug coverage (public vs private; $p < 0.0001$); prescribing physician specialty (GP vs specialist; $p < 0.0001$); and number and type of comorbid illnesses ($p < 0.01$).

Conclusion. Persistence to BP declined significantly over one year. Healthcare practitioners should take note of several factors when counselling patients taking BP for OP. (First Release Aug 15 2008; J Rheumatol 2008;35:1865–73)

Key Indexing Terms:
PERSISTENCE COMPLIANCE ADHERENCE OSTEOPOROSIS BISPHOSPHONATE

Maintaining health and preventing age-related diseases and the potentially-negative physical impacts of aging have become a major focus of many proposed health models[1]. Aging is associated with greater utilization of health services and medications. Notwithstanding, compliance with medication is critical in the management of older patients on longterm drug therapy for potentially disabling diseases. Compliance is composed of both adherence and persistence[2]. Further, adherence describes the extent to which a patient follows medical advice, such as a prescribed treatment regimen, while persistence is the total length of time that a given patient remains on therapy[3]. Poor adherence to therapy in patients with chronic, asymptomatic diseases is growing[4]. It has been estimated that at most 50% of patients adhere to longterm therapy, regardless of their disease or treatment[5]. Persistence rates from 62% to as low as 33% have been identified in patients taking hypertensive medications, with the largest decline in persistence occurring within the first 12 months after the initiation of therapy[6].

Poor adherence[7] is thought to be the main reason for the suboptimal therapeutic benefit of therapy[4]. Complications that arise from non-adherence with medication may lead to a decline in quality of life and associated increases in healthcare costs. A 1986 US estimate suggested that non-adherence to medications costs the US healthcare system up to $25 billion annually, through various expenditures associated with mortality, morbidity, and loss of productivity[7].

In Canada, roughly 1 in 4 women and 1 in 8 men over age 50 years has osteoporosis (OP)[8,9]. Both prevalence of OP and risk of fracture increase with age. OP accounts for 70% of the 25,000 hip fractures that occur each year in Canada, and these fractures are associated with increased mortality, high morbidity, and high costs[10]. Mortality within one year of sustaining a hip fracture is 20% higher than the rate in the normal population[10]. In terms of morbidity, 50% of women who sustain a hip fracture do not return to their previous functional state; about 20% require longterm care[8], and 6 months after sustaining a hip fracture, only 15% of patients

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are able to walk without an assistive device[11]. The resulting financial burden due to OP in Canada was $1.3 billion in 1993[9], much of this attributed to the consequences of fractures, especially hip fractures. Moreover, this expenditure is almost certain to increase as it is estimated that, by 2041, the annual number of hip fractures in Canada will more than triple, to about 88,000[9,11].

Bisphosphonates (BP) comprise a class of medication that has been shown in clinical trials to increase bone mineral density (BMD), decrease markers of bone turnover, and reduce the risk of OP-related fractures[12-18]. Further, the beneficial effects of BP, in terms of fracture risk reduction, have been demonstrated as early as 6 months after the initiation of treatment[19,20]. Oral BP risedronate and alendronate have demonstrated significant antifracture efficacy and are considered first-line treatments in the management of OP[9]. Despite this, few OP patients remain on therapy for more than one year, and the probability of remaining on OP treatment appears to decrease over time[21,22]. Persistence with BP has been found to be between 55% and 88% at 6 months, but to fall off to between 16% and 55% by 12 months[23-29]. This decline in BP use is clinically important, because poor adherence to OP medication has been demonstrated to have a negative effect on BMD and an increased risk of fractures[30].

Persistence with hypertensive and OP medications has been correlated with the complexity of the dosing regimen, patient age, number of medications for comorbid disorders, the number of comorbid diseases, cost of the drug, type and degree of nursing support, level of education about the disease, and specialty of the initially prescribing physician[3,7,21,22, 25,27,29,31-35].

We evaluated, in a large representative setting using a proprietary insurance claims database, the relationship between BP persistence and the following factors: (1) BP prescribed; (2) whether the current BP was the first OP drug used or a replacement for another non-BP drug (switched); (3) patient age; (4) type of patient drug coverage; (5) specialty of initial prescribing physician; and (6) number and type of comorbid diseases.

MATERIALS AND METHODS

Data source. Managed care plans or healthcare administrative databases and claims databases have become a common source for evaluating adherence to medications, including OP drugs, in large populations[26,35,36]. Such databases have advantages of being outside the realm of a controlled clinical trial (in which compliance tends to be high), and yet more objective and verifiable than patient or health care provider surveys. Consequently, the data for our study were acquired from a large Canadian public and private insurance claims database.

The Ontario Drug Benefits (ODB) plan covers about 2.2 million active claimants and pays for 68 million prescriptions annually in the Province of Ontario. The ODB claimant population comprises about 66% of seniors over age 65 years. Remaining claimants receive benefits through social assistance, disability, or catastrophic illness programs. The ODB public dataset includes 100% of all transactions from this plan. All claims are adjudicated online and transmitted monthly to Brogan Inc. under a data services agreement with the Ontario government. The Brogan Inc. private payer database consists of drug benefit claims paid by a group of private insurers. The private payer database, in total, collects information on over 10 million Canadians with 91 million prescriptions annually; 34% of records come from Ontario. These databases meet federal and provincial guidelines for patient and prescribing practitioner confidentiality. The records are anonymous, since the data suppliers scramble patient ID codes. ODB claims data have been validated in research and used for pharmacoepidemiologic studies on the use of OP, anti-hypertensive, and antibiotic medications[37-39].

Selection of patients. Each dataset was generated using only pay-direct claims. The data contained in our report were longitudinal. Each transaction was received with a scrambled and anonymous patient ID. The scrambled patient ID followed the individual for as long as he or she was part of the specific plan under which the data were received; it also allowed for the monitoring of patient utilization activity across time. Due to legal privacy restrictions, each dataset was acquired using groups of patients, as opposed to individual patient data. From the ODB and private payer databases, a retrospective study was performed, by selecting all new female patients who had initiated weekly BP therapy (risedronate 35 mg single tablet, once weekly, or alendronate 70 mg single tablet, once weekly) for OP, spanning the period from January 1, 2003 to February 28, 2006. Only female patients were included, in line with current indications for OP therapies. New users comprised 2 groups: (1) individuals for whom an OP medication had never been prescribed previously; and (2) individuals who, during the observation period, were switched from some other non-BP OP medication to either risedronate or alendronate.

Patients were subsequently classified into treatment groups, based upon the study drug they received, and were further classified by confounding factors associated with persistence, including (A) a switch from a previous OP medication (calcitonin, etidronate + calcium, raloxifene, parathyroid hormone, hormone replacement therapy) to risedronate or alendronate; (B) patient age (< 65 vs ≥ 65); (C) type of drug benefit coverage [private vs public (ODB)]; (D) among those receiving ODB coverage, those in longterm care versus those not in longterm care; (E) initial prescribing physician specialty [general practice, rheumatology, internal medicine, geriatrics, and other (all other specialties)]; and (F) type and number of comorbid conditions. Co-medications were determined by observing ± 90 days from dates of dispense data for an initiated BP. Patients in the comorbid groups were categorized into those having diabetes, cardiovascular (CV) disorders, or neurological disorders, based upon their use of any medication for one of these specific medical conditions (Table 1). Patients were tracked for any claim for a drug typically prescribed for any one of these comorbid categories of illness, and were flagged to the dispensing date of the BP index prescription.

Definition of persistence. The primary outcome was persistence, measured as the rate (percentage) of patients who continued taking a specific new BP, alendronate or risedronate, over a 12-month observation period. The patients were followed from their first claim for the specific target drug to their last claim during that 12 month period. The total days of therapy were then summed from start to finish, including the number of days supplied at the time of the patient's last claim. If a patient interrupted therapy for 30 days or more within the observation period, she was considered to be persistent only up to the end of the days supplied by the claim prior to interruption. Patients were scanned to ensure that they were active in the database for the entire observation period. Activity was determined by observing a claim submitted for any product. If no activity appeared for a patient throughout the observation period, that patient was not included.

Data analysis. Persistence was presented as the number of patients remaining persistent at 6 and 12 months post initial prescription. For the primary endpoint (time to failure-to-persist data), chi-square analysis was used to assess for statistically significant differences at 6 and 12 months, both within and between treatment groups, and relative to confounding factors asso-

Table 1. Definition of comorbidity by use of medication. Co-medication was recorded ± 90 days from the dispensing date of the initiating osteoporosis prescription.

Comorbidity	Medication
Diabetes	Avandia (rosiglitazone maleate), Actos (pioglitazone HCl), Avandamet (metformin HCl/rosiglitazone maleate), Glumetza (metformin HCl), metformin, Prandase (acarbose), Glucomex (metformin), Starlix (nateglinide), glyburide, Amaryl (glimepiride), Diamicron (gliclazide), chlorpropamide, tolbutamide, insulin
Cardiologic	Ace inhibitors, diuretics, calcium channel blockers, statins, angiotensin 2 receptor antagonists, beta blocker, anticoagulants, bile acid sequestrants, fibrates, Ezetrol (ezetimibe), Niaspan (niacin)
Neurologic	Tricyclics, benzodiazepines, non-benzodiazepines with indication for depression, Reminyl (galantamine HBr), Ebixa (memantine HCl), Parlodel (bromocriptine mesylate), Permax (pergolide mesylate), Mirapex (pramipexole dihydrochloride), Requip (ropinirole HCl), Prolopa (benserazide HCl/levodopa), Paxil (paroxetine HCl), Cipralex (escitalopram oxalate), Celexa (citalopram HBr), sertaline, fluoxetine, fluvoxamine, Wellbutrin (bupropion HCl), Effexor (venlafaxine HCl), Remeron (mirtazapine), 5-HTP, Aricept (donepezil HCl), Exelon (rivastigmine hydrogen tartrate), Sinemet (carbidopa/levodopa), Comtan (entacapone), selegiline

ciated with persistence (drug-switching, patient age, drug coverage, initiating physician, and comorbid conditions by medication). Regression analysis was performed to estimate the association between BP persistence and potential confounding factors. Significance was conservatively set at $p < 0.01$, to reduce the likelihood of type 1 error resulting from the multiple comparisons. Analysis was performed using MINITAB version 14.11.1.

RESULTS

Data from a total of 62,897 patients met study criteria and were analyzed. The number of patients in each group is provided in Table 2.

Regression analysis of type of BP, switching from prior OP medication, patient age, drug coverage, initiating prescriber specialty, and comorbid diseases as determined by comorbid medications demonstrated a significant quadratic inverse relationship ($p < 0.01$) between the number of patients on therapy and time. Examples of the regression curves are shown in Figures 1 to 3 for type of BP, switching to BP from another OP medication and age, respectively.

BP preparation prescribed. There was no statistically significant difference in the rate of persistence among those on risedronate (71.2%) versus those on alendronate (72.0%) at 6 months ($p = 0.11$). However, there was a significant difference at 12 months (54.4% vs 56.3%, respectively; $p < 0.0001$). This would not appear to be clinically significant.

Switching medications. For those who had switched from another non-BP medication for OP to either risedronate or alendronate, there was a significant difference between the rate of persistence for the 2 drugs at 6 months (71.5% vs 72.5%, respectively; $p < 0.01$), but not at 12 months (55.7% vs 56.4%, $p = 0.08$).

Age. Patients 65 or older who were taking either risedronate

Table 2. Number of patients by group.

Group	Risedronate	Alendronate
Medication	13766	23266
Switched from prior osteoporosis medication	29916	32981
< 65	5714	6504
≥ 65	24184	26450
Ontario Drug Benefits Plan	25417	28026
Private	4501	4955
Geriatrician	160	196
General practitioner	19487	21969
Internist	1694	1422
Other	3543	4068
Rheumatologist	538	367
Cardiovascular disorders (Car)	10842	12053
Car/neurologic disorders (Neu)	6745	7284
Diabetes mellitus (Dia)	95	104
Dia/Car	1239	1227
Dia/Car/Neu	759	744
Dia/Neu	50	55
Neu	3145	3426

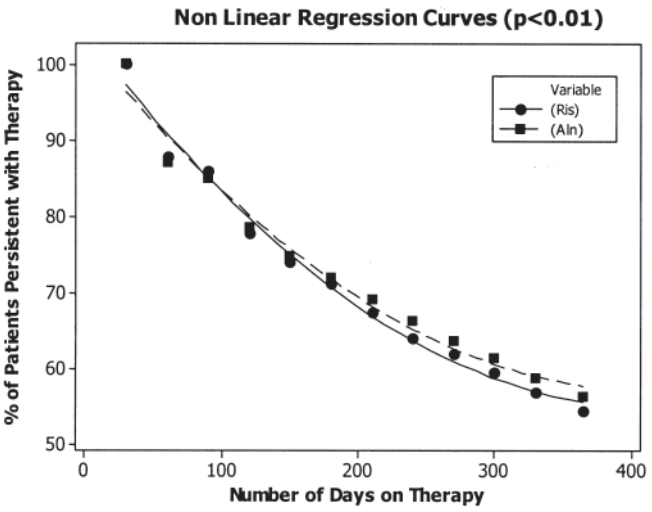

Figure 1. Regression curves for persistence with risedronate (Ris) or alendronate (Aln) over 12 months.

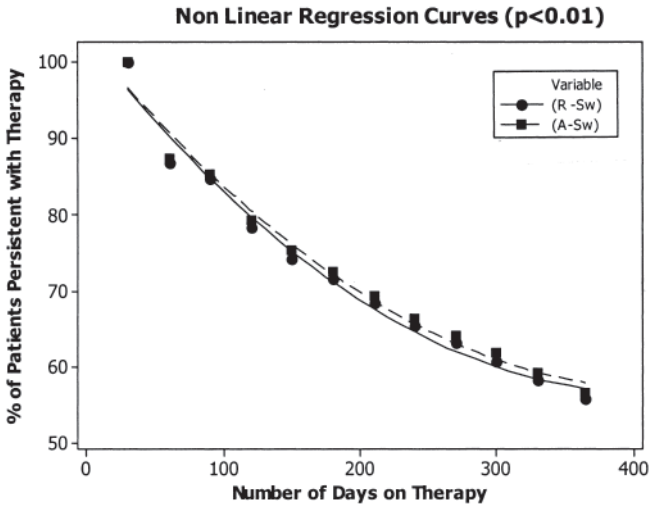

Figure 2. Regression curves for persistence over 12 months by patients who switched to risedronate (R-Sw) or aledronate (A-Sw) from a non-bisphosphonate medication for osteoporosis.

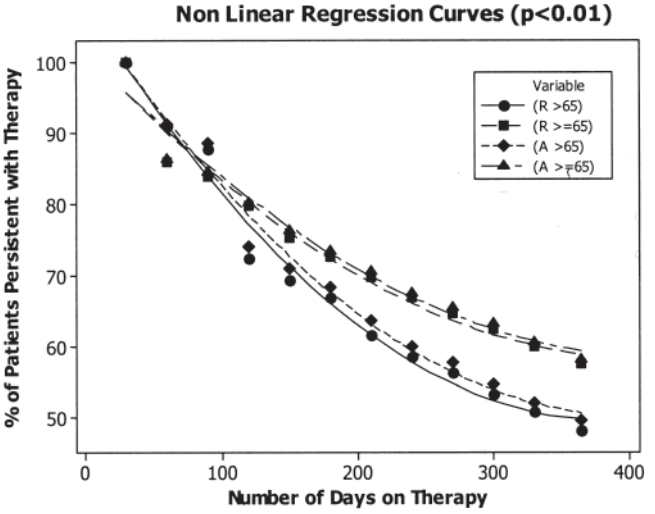

Figure 3. Regression curves for persistence of patients by age to risedronate (R) or alendronate (A) over 12 months (R: risedronate-Sw) or aledronate (A-Sw) from a non-bisphosphonate medication for osteoporosis

or alendronate were significantly more persistent ($p < 0.0001$) than those under age 65 at 6 months (67.0% vs 72.6%, 68.3% vs 73.5, respectively) and at 12 months (48.1% vs 57.5%, 49.5% vs 58.1%, respectively).

Drug coverage. The likelihood of continuing either drug, once started, was greater among those on ODB coverage than among those with private coverage, both at 6 and 12 months. Patients with ODB coverage taking risedronate were significantly more persistent ($p < 0.0001$) than patients with private coverage at both 6 months (72.4% vs 66.8%, respectively) and 12 months (57.3% vs 46.9%,); and the same was true for alendronate (73.1% vs 68.9%, and 57.8% vs 48.8%, respectively).

Longterm versus no longterm care. Among those on ODB coverage we were able to distinguish between those in longterm care versus those who were not. At 6 months, combining those receiving residronate 35 mg and those receiving alendronate 70 mg there were 4636 in longterm care of whom 3986 (86%) were persistent. This compared to 170,082 not in longterm care, among whom 66% were persistent with both risedronate and alendronate.

Chi-squared analysis revealed a strongly significant difference in persistence rate at 6 months between those in longterm care and those who were not (chi-squared = 795, df = 1; $p < 0.001$). At 12 months, 79% of the 3574 in longterm care remained persistent (80% on risedronate and 78% on alendronate, chi-squared = 2.97; df = 1; NS) compared to 50% of the 139,984 not in longterm care (chi-squared = 1.184; df = 1; $p < 0.001$).

Physician specialty. Patients prescribed BP by a general practitioner (GP) initially had greater persistence at 6 and 12 months than other specialties for either risedronate or alendronate (Table 3) while there were no significant differences by specialty between those taking risedronate or alendronate.

Comorbid diseases. Patient groups stratified by comorbid illness (CV and neurological diseases and diabetes) and combinations of these comorbid illnesses differed in their rates of persistence, as well. For example, persistence with risedronate at 6 months was significantly different between those with CV versus neurological disease (72.5% vs 68.1%; $p < 0.0001$), and between those with neurological versus both CV and neurological disease (68.1% vs 71.6%; $p < 0.0001$). At 12 months, there were differences between those with diabetes versus CV disease (38.9% vs 57.1%; $p < 0.001$); combinations of comorbid diseases also resulted in differences in persistence.

In contrast to risedronate, alendronate persistence was not affected by the presence of diabetes alone. Persistence with alendronate at 6 months was significantly higher in those with CV versus neurological disease (74.4% vs 68.3%; $p < 0.0001$); CV versus diabetes and CV disease (74.4% vs 70.8%; $p < 0.001$); CV versus CV and neurological disease (74.4% vs 70.4%; $p < 0.0001$); and CV disease versus all 3 (74.4% vs 67.9%; $p < 0.0001$). At 12 months, similar effects of combinations of CV diseases were observed; however, in contrast to risedronate, alendronate was not affected by the presence of diabetes alone at either time point.

Comparing persistence rates by comorbid condition between those on risedronate and those on alendronate, a significant difference in persistence was observed in patients with CV comorbidity (72.5% vs 74.4; $p = 0.001$) and 12 months (57.1% vs 58.9%; $p < 0.01$).

DISCUSSION

We demonstrated a significant decline in persistence to BP

Table 3. Six and 12-mo chi square significance test: persistence versus specialty of initial prescribing physician.

Risedronate Persistence, 6 mo				Risedronate Persistence, 12 mo			
Specialty	%	Significance, p < 0.01		Specialty	%	Significance, p < 0.01	
Rheum	64.3	0.6750	N	Rheum	46.3	0.2067	N
Geri	62.5			Geri	40.1		
Rheum	64.3	< 0.0001	Y	Rheum	46.3	< 0.0001	Y
GP	72.0			GP	56.0		
Rheum	64.3	0.5620	N	Rheum	46.3	0.5016	N
IM	62.9			IM	44.6		
Rheum	64.3	0.0430	N	Rheum	46.3	< 0.0001	Y
Other	59.7			Other	37.0		
Geri	62.5	0.0080	Y	Geri	40.1	< 0.0001	Y
GP	72.0			GP	56.0		
Geri	62.5	0.915	N	Geri	40.1	0.3318	N
IM	62.9			IM	44.6		
Geri	62.5	0.4830	N	Geri	40.1	0.3278	N
Other	59.7			Other	37.0		
GP	72.0	< 0.0001	Y	GP	56.0	< 0.0001	Y
IM	62.9			IM	44.6		
GP	72.0	< 0.0001	Y	GP	56.0	< 0.0001	Y
Other	59.7			Other	37.0		
IM	62.9	0.026	N	IM	44.6	< 0.0001	Y
Other	59.7			Other	37.0		
Alendronate Persistence, 6 mo				**Alendronate Persistence, 12 mo**			
Specialty	%	Significance, p < 0.01		Specialty	%	Significance, p < 0.01	
Rheum	69.2	0.1900	N	Rheum	49.9	0.0514	N
Geri	63.8			Geri	41.1		
Rheum	69.2	0.2760	N	Rheum	49.9	0.0323	N
GP	71.8			GP	55.4		
Rheum	69.2	0.2500	N	Rheum	49.9	0.4530	N
IM	66.0			IM	47.7		
Rheum	69.2	0.0020	Y	Rheum	49.9	< 0.0001	Y
Other	61.1			Other	36.9		
Geri	63.8	0.0130	N	Geri	41.1	< 0.0001	Y
GP	71.8			GP	55.4		
Geri	63.8	0.5320	N	Geri	41.1	0.0925	N
IM	66.0			IM	47.7		
Geri	63.8	0.4550	N	Geri	41.1	0.1971	N
Other	61.1			Other	36.9		
GP	71.8	< 0.0001	Y	GP	55.4	< 0.0001	Y
IM	66.0			IM	47.7		
GP	71.8	< 0.0001	Y	GP	55.4	< 0.0001	Y
Other	61.1			Other	36.9		
IM	66.0	0.0010	Y	IM	47.7	< 0.0001	Y
Other	61.1			Other	36.9		

Geri: Geriatrician, GP: General practitioner, IM: Internal medicine, Rheum: Rheumatology, Other: All other specialties).

over 6 and 12 months. Using a maximum 30-day gap between refill expiry and the next refill as the definition of non-persistence, persistence rates varied between 59.7% and 73.5% at 6 months, and between 37.0% and 58.9% at 12 months, depending upon the subject group studied. Prior studies of persistence with OP medications have demonstrated variability in persistence rates, in part based upon the number of days allowed for the refill gap. Despite differences in study design, the data in our study are consistent with earlier studies, which have demonstrated persistence rates between 55% and 88% at 6 months, and between 16% and 55% at 12 months[23-29,35,40-43]. Weycker, *et al*[44] determined that the largest decline in persistence occurs during the first 12 months after initiation of therapy, with subsequent slowing of discontinuation up to 3 years. The percentage of women who had discontinued therapy in their study was 47% at 1 year, and 77% at 3 years. In 3 other studies, evaluating persistence over a 2-year period, between 40% and 80% of women discontinued therapy[27,40,41]. In light of published studies suggesting that low persistence with OP

drug therapy is associated with increased fracture risk[43], the results of our study indicate that, at least in Ontario, a large number of women with OP are not adequately protected against future OP-related fractures[21,40,41].

A second objective of our study was to identify variables that were related to the discontinuation of therapy. Tosteson, *et al*[29] conducted a random telephone survey of 956 women over age 45 and with a T-score of < –1.0 who had initiated treatment with an OP medication. Factors associated with increased likelihood of discontinuation were medication side effects and a poor understanding of bone mineral test results. Women who did not know their BMD results or presumed the results were normal were more likely to discontinue therapy. Patients who exercised regularly and demonstrated a willingness to take prescribed medication were more likely to remain persistent. The authors concluded that persistence with OP therapy may be improved by (a) minimizing side effects by tailoring medications to the patient's attitude towards treatment side effects, and (b) increased education regarding BMD test results. Similarly, Carr, *et al*[45] completed a survey of 533 women over the age of 50 years and observed a one-year adherence to therapy was 48% while non-persistence was associated with concern over medication side effects, difficulty taking the medication (dosing intervals), and dissatisfaction with the medication. Patients who had had a fracture were more likely to adhere to therapy.

Clowes, *et al*[3] randomized 75 postmenopausal women to a no-monitoring group, a nurse monitoring group, and a nurse monitoring plus regular urine N-telopeptide testing group. These authors observed a 57% increase in adherence and a 25% increase in persistence in patients who were monitored by a nurse. Pickney, *et al*[34] followed 341 patients who were informed of their BMD results and treated following their first BMD test. Forty-one percent of patients had discontinued treatment at one year, most commonly due to side effects and the cost of medication. Patients who correctly recalled their BMD score were more likely to have remained on the prescribed medication. Hence, patient knowledge of BMD may be helpful as an adherence strategy.

In our study, persistence with treatment was significantly associated with type of BP prescribed, whether BP was the first drug used for treatment of OP or a replacement for another non-BP OP drug, patient age, type of drug coverage, initiating physician specialty, and number and type of comorbid diseases. This, taken with previous studies[46] may suggest that patients with comorbid diseases have more interest in their health, are more likely seen by a health professional, and are more likely to know their BMD and adhere to therapy. Our study was the first to demonstrate a difference, albeit small, in persistence between the 2 weekly oral preparations, risedronate and alendronate. These results are in contrast to Curtis, *et al*[47], who evaluated persistence with risedronate and alendronate in patients taking glucocorticoids and found no significant differences between the 2 therapies. Further, Rossini, *et al*[48] found a significant difference in persistence with once-weekly alendronate versus all other medications available in Italy, including risedronate; however, patients in that study used once-daily risedronate, as opposed to weekly risedronate. This suggests as supported by other studies, that persistence with weekly BP is greater than with daily BP[15,22,25,47-49]. Hence, the difference between alendronate and risedronate noted by Rossini, *et al*[48] may have been the result of the dosing schedule rather than the drug.

Our study also evaluated whether switching to a BP from another OP drug, versus having the BP being the first line drug, had an influence on persistence. We demonstrated a small difference in persistence at 6 months between risedronate and alendronate in patients who had switched from a previous OP medication. However, there was no difference seen at 12 months. This result could be related to the drug coverage plans as were in place at the time in Ontario. Typically, patients had to fail another OP therapy before acquiring drug coverage for either alendronate or risedronate. We could not identify previous studies regarding switching of medications and subsequent persistence to BP. In other therapeutic areas such as hypertension and dyslipidemia and in contrast to the results of our study, Thiebaud, *et al*[50] observed that switching statin medications substantially reduced the likelihood of patient compliance. However, Perreault, *et al*[33] found a persistence rate of > 70% in patients who had changed medication classes for treatment of hypertension. It may be that statins were switched secondary to side effects, whereas BP may have been switched secondary to poor response; further investigation is needed.

In a study of over 1500 patients, Papaioannou, *et al*[51] found that increasing patient age had a significant positive effect on persistence with OP medication. Penning-van Beest, *et al*[28] and Curtis, *et al*[47] similarly found that younger age had a negative influence on persistence with OP medication, which is similar to reports for anti-hypertensive medications[32]. Our study supports the results observed in these studies. Specifically, significantly more patients age 65 and older persisted with either risedronate or alendronate than did those under age 65, at both 6 and 12 months. In contrast, Solomon, *et al*[35] studied persistence with OP medication in 40,000 patients and found that increasing age had a negative influence on persistence. However, patients in that study included residents of longterm care centers where they have exhibited higher rates of persistence[35]. The average age of patients in Ontario longterm care centers is 86 years[52]. If a large number of longterm care patients were included in the analysis, it could be speculated that the persistence rate in the 65 and older group could be artificially inflated. Alternatively, the positive relationship between persistence and increasing age could be due to the fracture sta-

tus of patients. Studies have indicated that the risk of osteoporotic fractures increases with age[9]. Further, the presence of osteoporotic fracture has been associated with increased persistence with OP therapy[35]. If older patients had more fractures, then one could assume that an analysis of this cohort would demonstrate a positive relationship between persistence and increasing age.

We were not able to identify studies that addressed the impact of drug coverage on persistence with OP medication between 1975 and 2005. Our findings suggest that persistence is significantly influenced by a patient's type of drug coverage. There was a significant difference, about 5.0%–6.0%, in persistence with medication in patients with drug coverage by the ODB formulary versus those who had private coverage, at both 6 and 12 months. The results were not influenced by the type of OP medication that a patient was taking. Further, the results by drug coverage are similar to the results for age. In Ontario, government coverage (ODB) starts at age 65. Since patients over 65 were more persistent than those under 65, it is possible that age had a positive effect on persistence among those with public coverage. The converse may also be true, whereby public coverage may have a positive effect on persistence among those over 65. Hence, the interaction of persistence to OP medication with age and drug coverage warrants further investigation. Patients with hypertension who receive social assistance are more likely to persist with hypertensive medications than those without social assistance[33]. The ODB formulary is similar to a social assistance program, in that it provides medications for those without other coverage. This may support the observations of persistence in patients with ODB versus private coverage in this study.

Previous studies have indicated that the specialty of the prescribing physician could influence persistence with OP medication. Rossini, *et al*[48] and Pickney, *et al*[34] found that persistence with OP medication in the US was significantly lower when the drug was prescribed by a general practitioner, orthopedic surgeon, or a gynecologist versus an internist. Our findings conflict with these aforementioned studies. Generally, patients in our study were more likely to remain persistent to either risedronate or alendronate when it was prescribed by a general practitioner versus any other specialty, at both 6 and 12 months. Persistence also was significantly greater in patients prescribed their BP by a rheumatologist or internist versus other physicians, except geriatricians. The differences with our findings and those above may be due to the type of patients managed by different physicians in these settings (US and Canada). For example, in Canada patients receive their care and prescriptions mostly from a GP, while patients with specific medical conditions in the US may not. Further, patients tend to see GP more often than specialists, as GP are the first point of contact for illness or potential illness in the healthcare system in Canada. In a study of hypertension, a higher number of physician visits was positively associated with increased persistence[53]. This could explain the differences in persistence between specialists and general practitioners in our population.

Some studies[47,35] have demonstrated that type and number of comorbid conditions and number of medications prescribed for these conditions may negatively affect persistence in patients with OP. Our study found a significant negative trend between number of comorbid conditions and persistence. That this trend was not observed for all disease combinations, could be attributed to the lack of numbers and statistical power for certain disease combinations. Studies in hypertension have also observed an inverse relationship between number of different classes of anti-hypertensive medications and persistence. Taken together, it could be that patients with multiple diseases taking multiple medications could be more ill. As a result, they may have difficulty maintaining persistence with multiple, complex dosing regimens. Further, patients with asymptomatic diseases like hypertension and OP may misunderstand their disease, including the need for regular medication in the absence of symptoms. The interaction of asymptomatic-symptomatic diseases and medication persistence requires further investigation.

Patients with CV disease, either alone or in combination with other comorbid conditions, were more persistent with their BP than patients in other comorbidity categories. The higher rate of persistence in the groups with CV disorders might be secondary to an increased number of patient visits, since patients with CV disorders tend to see their physicians more often[53,54].

Limitations. Strengths of our study include large sample size from a setting reflecting those seen in practice, thus improving generalizability of results. In contrast, clinical trials set restrictive entry criteria and geographic representation. Some limitations warrant consideration. First, databases such as the ODB are constructed primarily to provide cost analysis and do not necessarily contain all relevant clinical information, such as the results of BMD tests, fracture status, or patient historical data and physical findings. Second, the data we utilized were grouped and hence patient data did not allow us to examine reasons for discontinuation during treatment, such as side effects. Further, we were unable to analyze simultaneous, multiple variables that could determine persistence within a single patient. A third limitation is that recording of incorrect drug initiation dates could result from the initial prescriber providing medication samples prior to a prescription being written. Finally, we cannot verify whether patients in the database actually took their medication, or whether they took the appropriate dose as prescribed. Despite these shortcomings, healthcare databases generally have been demonstrated to be a reliable estimate of medication consumption[55].

In summary, BP medication persistence appears to decline significantly over 12 months despite the presence of

evidence based recommendations and effective medications. Determinants of persistence include patient age, type of drug coverage, choice of prescribed BP medication, types and number of comorbidities, and specialty of the prescribing physician. Hence, patients and providers should be educated and provided strategies regarding importance of persistence to BP. Being alerted to the determining factors as observed in our findings may help them to do so.

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