Osteoporosis International (2019) 30:2311–2319
https://doi.org/10.1007/s00198-019-05061-z

ORIGINAL ARTICLE

Time trends in oral bisphosphonate initiation in Ontario, Canada over 20 years reflect drug policy and healthcare delivery changes

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Received: 23 November 2018 / Accepted: 14 April 2019 / Published online: 17 July 2019

Abstract

Summary Characteristics of patients starting oral bisphosphonate therapy changed over time, reflecting trends in osteoporosis management (e.g., new drugs to market), and general healthcare delivery (e.g., benzodiazepine use declined, statin use increased). When designing studies that examine osteoporosis drug effects, potential time-related biases must be considered.

Introduction To describe the type of oral bisphosphonate initiated and characteristics of patients starting oral bisphosphonate therapy over time.

Methods We identified community-dwelling older adults (ages ≥ 66 years) initiating oral bisphosphonate therapy from April 1996 to March 2016 (1996 to 2015 fiscal years) using healthcare administrative data in Ontario. Patients with conditions other than osteoporosis that may impact bisphosphonate prescribing were excluded. The bisphosphonate initiated and patient characteristics were summarized by fiscal year and stratified by sex.

Results We identified 560,817 eligible patients (81% women). Most patients initiated cyclical etidronate from 1996 until 2005, and then weekly regimens became dominant. In 2008, risedronate became the main oral bisphosphonate (46% risedronate, 43% alendronate, 11% etidronate); with its use increasing after availability of monthly and delayed-release risedronate formulations. In 2015, 71% of patients started risedronate, 28% started alendronate, and less than 2% started etidronate. Characteristics of patients changed over time, reflecting changes in osteoporosis management and general healthcare delivery. Over time, a larger proportion of men (9% to 28%) and patients with diabetes (women 10% to 17%, men 14% to 22%) initiated therapy; benzodiazepine (women 22% to 13%, men 20% to 10%) and estrogen-based hormone replacement therapy (12% to 15% of women 1996–2002 to 3% since 2008) decreased, while statin use increased (women 15% to 39%, men 14% to 52%).

Conclusions The characteristics of patients starting oral bisphosphonate therapy have changed over time. Consideration must be given to these time trends when designing studies that examine osteoporosis drug effects.

Keywords Drug therapy · Epidemiology · Health services research · Osteoporosis · Pharmacoepidemiology · Practice patterns

Introduction

Canada has provincially distributed universal Medicare for all residents that covers medically necessary physician services, such as hospital and outpatient visits. In Ontario, the most populous province of Canada, all prescriptions on the provincial formulary are covered for residents aged 65 years or older. This includes oral bisphosphonates (alendronate, etidronate,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-019-05061-z) contains supplementary material, which is available to authorized users.

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and risedronate), denosumab, raloxifene, and zoledronic acid [1–3]. Previous analyses that examined patients starting their first osteoporosis medication in British Columbia and Ontario from 1996 to 2008 showed that over 99% of patients in Ontario received an oral bisphosphonate [1]. Indeed, initial treatment with or intolerance to oral bisphosphonate is required for coverage of denosumab and zoledronic acid in Ontario [2, 3]. Therefore, oral bisphosphonates remain the first line of osteoporosis therapy in Ontario, despite Canadian osteoporosis clinical practice guidelines including denosumab, hormone therapies, raloxifene, and zoledronic acid as first-line treatment for various patient groups [4]. Nonetheless, drug coverage of different oral bisphosphonates has changed over time in Ontario. For example, etidronate has been available unrestricted since 1996, yet alendronate and risedronate were only available under limited use until 2007 [1]. In addition, new formulations of alendronate (e.g., weekly + vitamin D) and risedronate (e.g., monthly and weekly delayed release) have come to market [5, 6].

The introduction of new therapeutic options, updates to practice guidelines, and healthcare policy changes may influence the type of oral bisphosphonate initiated as well as the characteristics of patients receiving drug therapies over time. Changes in patient characteristics and risk factors can greatly impact studies of drug effects, particularly in choosing optimal comparator groups [7]. For example, in the first years of intravenous (IV) bisphosphonate availability in the USA, patients receiving IV osteoporosis treatments were at higher fracture risk (e.g., more likely to have experienced a fracture and have more comorbid conditions) compared to patients starting oral bisphosphonates. However, the relationship between fracture risk profile and the choice to use IV bisphosphonates attenuated over time [8]. The authors emphasized that these trends should be considered in studies of the absolute and comparative effectiveness of these medications in this population [8]. In Canada, it was demonstrated that drug policy-induced trends in the type of bisphosphonate initiated likely resulted in selection biases [9], and Ontario drug formulary generic substitution policies yielded fluctuations in oral bisphosphonate use, particularly as new brand alternatives were added to the public formulary [5, 6]. The purpose of our study was to describe the type of oral bisphosphonate initiated and compare the characteristics of patients initiating oral bisphosphonate therapy in Ontario, Canada over time and by sex.

Methods

Data source

In Ontario, all residents receive universal healthcare coverage for medically necessary services and procedures. In addition, coverage of drugs listed on the provincial formulary is provided to seniors (65 years of age or older) and those on social assistance. Thus, among seniors, a complete medical history is available by linking ambulatory, inpatient, outpatient, primary care, and pharmacy records. These datasets were linked using unique encoded identifiers and analyzed at ICES. We identified all seniors 65 years of age or older who initiated any osteoporosis drug between April 1, 1996 and March 31, 2016: bisphosphonates (alendronate, cyclical etidronate, risedronate, and zoledronic acid), denosumab, nasal calcitonin, and raloxifene. Teriparatide is not covered under the Ontario provincial drug plan and was not considered. Fiscal year was defined according to that of the Ontario government: April 1 to March 31 (e.g., the 1996 fiscal year included patients whose first osteoporosis drug was dispensed between April 1, 1996 to March 31, 1997). Medical and pharmacy claims within the year prior to first osteoporosis drug dispensation were used to characterize patients (e.g., demographics, healthcare utilization, and medication use). We excluded patients with data errors (i.e., death date prior to dispensation date), and to increase the probability that patients received bisphosphonate therapy for osteoporosis, we excluded patients with a diagnosis for other conditions that may have an alternate bisphosphonate dosing: celiac disease, Cushing's syndrome, hypercalcemia, hyperparathydroidism, malignant neoplasm, organ transplant, osteomalcia, osteopetrosis, Paget's disease, renal impairment, or dialysis. We then restricted inclusion to patients aged at least 66 years at first prescription (to ensure at least 1 year of drug plan eligibility), community-dwelling residents, and patients initiating oral bisphosphonate therapy as their first osteoporosis medication.

Data analysis

The number of patients starting therapy and the percent of patients initiated on each drug (molecule and formulation) were plotted by fiscal year. Patient characteristics were summarized using descriptive statistics (proportions for categorical variables and means with standard deviations for continuous variables) by sex and fiscal year. Preliminary results indicated little change annually for most characteristics; therefore, 5-year groupings were used to describe overall trends. However, clear annual trends were noted for benzodiazepine, statin, gastrointestinal drug, and hormone therapy use and thus respective proportions of patients with use were plotted by fiscal year. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Ethics

This study was approved by the Research Ethics Boards at Sunnybrook Health Sciences Centre in Toronto and the University of Toronto.

Results

Number of new patients and drug initiated

We identified 807,489 patients initiating an osteoporosis drug for the first time in Ontario from 1996 to 2015, Fig. S1 available as an online supplement. We then excluded the following patients: missing age or death before prescription date (n = 243), health exclusions (n = 28,434), age less than 66 years (n = 173,744), and long-term care residents (n = 29,040). After exclusions, 576,028 eligible seniors initiating osteoporosis therapy remained. Of these, 560,817 (97% of eligible patients starting osteoporosis therapy) initiated an oral bisphosphonate and were included.

The number of patients starting an oral bisphosphonate increased annually from 12,278 patients in 1996 to 38,106 patients in 2001, then remained relatively stable from 2001 to 2007 (average annual number of patients = 36,113) (Fig. 1). A 23% relative decrease in the number of patients starting an oral bisphosphonate was seen between 2007 and 2008 (from 35,746 to 27,657 patients), followed by a 17% decrease between 2010 and 2011 (from 23,757 to 19,679 patients). The number of patients starting therapy then stabilized from 2012 through 2015 (average annual number of patients = 18,886).

Etidronate remained nearly exclusive until 2000 (Fig. 2); as it was the only drug available on the public formulary until November 2000 (Table 1). Alendronate and risedronate were first used in 2000 and 2001, respectively. Alendronate was the main weekly bisphosphonate used through 2007, then risedronate became the most common oral bisphosphonate in 2008 (46% risedronate, 43% alendronate, 11% etidronate). Risedronate use rose steadily since 2008, particularly after monthly (2009/06), and weekly delayed-release (2012/02) risedronate formulations were added to the formulary. In 2015, 28% of patients initiated alendronate formulations, 71% initiated risedronate formulations, and less than 2% initiated etidronate.

Patient characteristics and medication use

Table 2 summarizes patient characteristics by 5-year fiscal year groupings, with results summarized by fiscal year provided in the supplementary materials, Tables S1 (women) and S2 (men). Age (mean age of women 74.9 years [SD 6.8]; mean age of men 76.2 years [SD 6.8]) and rurality of residence remained stable over time. However, a larger proportion of men (from 6% in 1996 to 28% in 2015) and patients with diabetes (women 10% to 17%, men 14% to 22%) initiated therapy over time. A consistently higher proportion of men (21% overall) had oral glucocorticoid use than women (9% overall). The proportion of patients receiving an opioid prescription in the year prior to index decreased modestly between 1996/04-2001/03 and 2011/04-2016/03 (women 31% to 27%, men 42% to 33%).

Of interest, history of benzodiazepine use in the year prior to starting oral bisphosphonate therapy decreased over time (women 27% to 11%, men 23% to 10%) (Fig. 3a), while statin use increased over time, especially among men (women 10% to 39%, men 8% to 54%) (Fig. 3a). Hormone therapy use in women remained stable from 1996 until 2001 (around 12% of women), then there was a modest increase in use in 2002 (to 15% of women). Between 2002 and 2007, there was a steady decrease in use (from 15% to 4%); then, from 2008 to 2015, use remained stable at 3% (Fig. 3a). A shift in gastroprotective drug use was also observed: histamine-2 receptor antagonist (H2RA) use decreased (women 21% to 3%, men 22% to 4%),

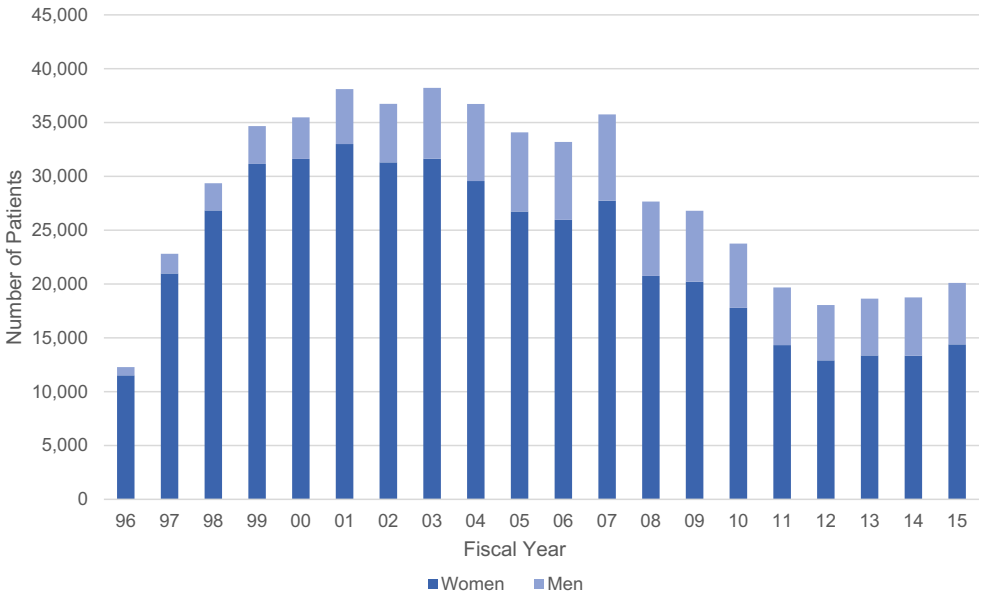

Fig. 1 Number of patients starting bisphosphonate therapy by sex and fiscal year

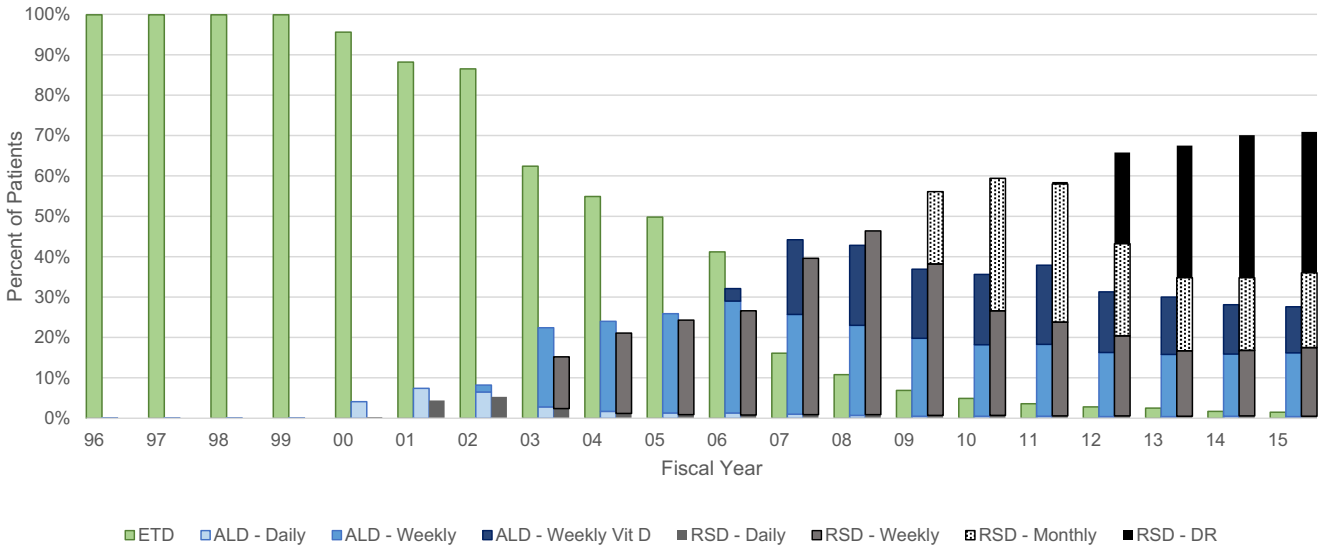

Fig. 2 Proportion of patients starting each bisphosphonate formulation by fiscal year. *Etidronate (ETD): left panel. Alendronate (ALD): middle panel. Risedronate (RSD): right panel*

while proton pump inhibitor (PPI) use increased (women 7% to 27%, men 9% to 32%) (Fig. 3b).

Discussion

We studied 560,817 patients starting bisphosphonate therapy in Ontario from 1996 to 2016 and identified changes over time in the number of patients initiating therapy, type of bisphosphonate initiated, and the proportion of men treated. We also found a decline in benzodiazepine, H2RA, and hormone therapy use and an increase in statin and PPI use. Time trends likely reflect changes in osteoporosis management and general healthcare delivery. First, the number of patients starting oral bisphosphonate therapy in Ontario increased from 1996 to 2000 and peaked between 2001 and 2007, with two periods of decline after 2008. The decline in number of patients starting therapy may relate to drug safety announcements on the use of bisphosphonates released in 2005 (osteonecrosis of the jaw), 2007 (atrial fibrillation), and 2010 (atypical fractures) in the USA, as well as a Health Canada safety inquiry in 2011 [11, 12]. These warnings were followed by media coverage associated with a decline in bisphosphonate use in the USA and Australia [13–15]. Of interest, the average age of patients initiating bisphosphonate therapy remained stable over the 20-year study period; this finding is consistent with a stable age distribution among Ontario's senior population from 1996 to 2011, per the Canadian census [16–19].

Our results show major time trends in the most common oral bisphosphonate initiated, related to Ontario public drug coverage [3]. Prior analyses in British Columbia and Ontario identified that physicians prescribe according to practice

Table 1 Notice of compliance dates for oral bisphosphonates and current public formulary listing status on Ontario

Bisphosphonate	Strength	Regimen	Notice of compliance[a] [10]	Ontario Drug Benefit formulary listing status (date of listing) [3]	Periods of limited use under Ontario Drug Benefit (restricted access) [1]
Etidronate and calcium	400/500 mg tab	14 days oral etidronate then 76 days oral calcium	19 Jul 1995	General benefit (Oct 1996)	
Alendronate	5 mg tab	Daily	10 Sep 1997	Not listed	Nov 2000–Jan 2007
	10 mg tab	Daily	18 Dec 1995	General benefit (Jan 2007)	Jan 2003–Feb 2007
	70 mg tab	Weekly	04 Feb 2002	General benefit (Jan 2007)	
	70 mg/75 mL solution	Weekly	19 Jan 2004	Not listed	
	70 mg + 70 μg D_3 tab	Weekly	03 Feb 2006	General benefit (Jan 2007)	
	70 mg + 140 μg D_3 tab	Weekly	06 Aug 2008	General benefit (Jun 2009)	
Risedronate	5 mg tab	Daily	17 Jul 2000	General benefit (Jun 2007)	Mar 2001–Jun 2007
	35 mg tab	Weekly	09 Dec 2002	General benefit (Jun 2007)	Apr 2003–Jun 2007
	150 mg tab	Monthly	24 Sep 2008	General benefit (Jun 2009)	
	35 mg tab (delayed release)	Weekly	27 Jul 2011	General benefit (Feb 2012)	

[a] Approval by Health Canada for marketing in Canada

Table 2 Characteristics of patients starting bisphosphonate therapy, stratified per 5 fiscal years (N = 560,817)

	Apr 1996–Mar 2001		Apr 2001–Mar 2006		Apr 2006–Mar 2011		Apr 2011–Mar 2016	
	Women N = 122,108	Men N = 12,474	Women N = 152,231	Men N = 31,624	Women N = 112,427	Men N = 34,730	Women N = 68,324	Men N = 26,899
Age (years), mean ± SD	74.8 ± 6.3	75.5 ± 6.3	75.3 ± 6.7	75.9 ± 6.5	74.7 ± 7.0	76.2 ± 6.8	74.6 ± 7.3	76.7 ± 7.2
Rurality Index for Ontario								
Urban	75.6%	74.0%	71.6%	74.7%	70.7%	74.4%	70.3%	71.2%
Non-major urban	18.7%	19.4%	21.9%	19.6%	22.9%	20.4%	23.0%	22.7%
Rural	5.2%	6.0%	5.8%	5.1%	5.8%	4.7%	5.6%	5.2%
Missing	0.5%	0.6%	0.7%	0.6%	0.6%	0.5%	1.1%	0.8%
Emergency visits, any[a]	N/A	N/A	30.3%	37.6%	33.5%	40.6%	34.2%	41.0%
Hospital visits, any[a]	14.3%	25.6%	14.8%	22.9%	15.1%	22.6%	15.1%	22.6%
BMD test in past year	63.0%	48.3%	68.8%	61.3%	68.9%	62.6%	68.1%	62.3%
Prior hip fracture[b]	1.5%	2.2%	2.1%	2.9%	2.6%	3.6%	3.3%	4.3%
Comorbid conditions								
Angina/MI/DVT/PE	16.6%	25.5%	14.0%	22.9%	11.5%	20.4%	8.8%	17.5%
Asthma	6.9%	11.0%	5.5%	7.6%	4.6%	5.9%	4.3%	4.6%
Chronic obstructive pulmonary disease	6.8%	19.3%	6.1%	15.3%	5.9%	12.7%	6.3%	12.0%
Diabetes	9.6%	13.5%	11.7%	15.6%	15.6%	20.0%	17.0%	21.8%
Gastroesophageal reflux disease	3.0%	3.5%	2.5%	3.1%	2.2%	3.1%	2.6%	2.7%
Hypercholesterolemia	11.3%	8.9%	12.5%	12.3%	12.0%	12.4%	10.2%	10.8%
Other drug use								
Benzodiazepine	21.9%	19.7%	18.4%	15.2%	15.6%	12.3%	13.0%	10.1%
Estrogen-based hormone replacement therapy	11.9%	–	9.6%	–	3.5%	–	3.2%	–
Histamine-2 receptor antagonist	16.2%	20.3%	10.4%	12.6%	5.1%	6.4%	3.1%	4.0%
Opioid	31.1%	42.0%	27.6%	36.0%	27.5%	34.6%	27.3%	33.3%
Oral glucocorticoid	9.3%	25.9%	8.1%	19.3%	9.1%	18.7%	11.8%	22.2%
Proton pump inhibitor	7.3%	8.9%	13.7%	15.8%	21.4%	24.7%	26.1%	29.6%
Selective serotonin reuptake inhibitors	5.7%	5.3%	7.2%	6.0%	7.8%	6.4%	9.4%	7.7%
Statin	14.7%	13.7%	25.6%	30.8%	35.1%	45.0%	39.2%	52.3%
Tricyclic antidepressants	5.7%	3.8%	4.9%	3.4%	4.6%	2.9%	4.1%	2.8%

BMD bone mineral density, MI myocardial infarction, DVT deep vein thrombosis, PE pulmonary embolism, N/A not available or suppressed due to small cell size

[a] Emergency department visits and hospitalizations were recorded separately. Emergency department services only recorded since April 2001

[b] Only captures hip fractures ascertained through hospitalization discharge records, so may underrepresent total hip fracture history

guidelines within the limits of drug formulary listing, and thus switched to first-line therapies (alendronate, risedronate) once listed on provincial formularies [1]. Alendronate was approved in Canada in the same year as etidronate (1995) but did not gain general benefit through the Ontario public drug formulary until January of 2007. Similarly, risedronate gained general benefit access in June 2007. Prescribing preferences immediately changed to favor alendronate and risedronate once open-listed in 2007. Relative use of risedronate over alendronate increased dramatically from 2008 through 2015, likely due to the availability of four different formulations available for use (daily, weekly, weekly delayed-release, and monthly) compared to only three formulations with alendronate (daily, weekly, and weekly with vitamin D). Of interest, the finding that risedronate is prescribed preferentially over alendronate in Ontario contrasts with prescribing practices in the USA [20] and other regions [21] where alendronate use is more prominent. We speculate that this may be due, in part, to strategic marketing of risedronate in Canada between 2000 and 2011 coupled with caution towards the gastrointestinal safety of generic bisphosphonates. Ontario has a generic substitution policy, and risedronate offered more dosing options and brand formulations, which may impact prescribing. Prior research identified a shift from alendronate

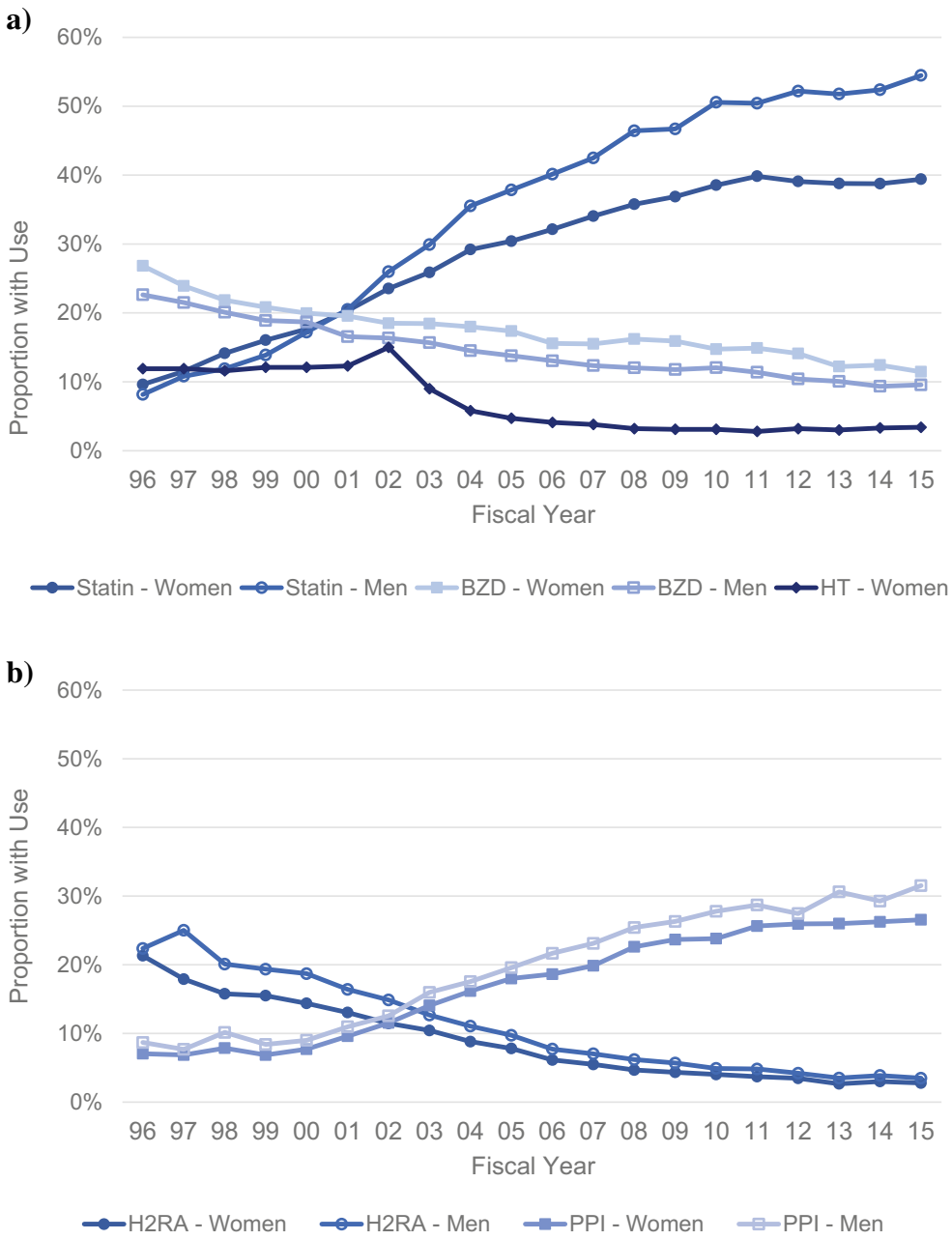

Fig. 3 Proportion of patients with **a** benzodiazepine (BZD), statin, and hormone therapy (HT) use; **b** proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) use; within year prior to initiation of oral bisphosphonate therapy, by sex and fiscal year

generic prescriptions to risedronate brand prescriptions in Ontario from 2002 to 2013 [6].

We also document changes in patient characteristics over time, demonstrative of changes in osteoporosis management and general healthcare delivery. In particular, notable changes were seen in the proportion of patients who received drugs affecting fracture risk. For example, a decrease was seen in history of benzodiazepine and opioid use, medication classes associated with increased falls risk in older adults [22–25]. The decline in benzodiazepine use can primarily be explained by the deprescribing movement of benzodiazepines over the last 20 years; benzodiazepine deprescribing guidelines were published in 2016 in Ontario [23], but benzodiazepines have been listed in the Beers Criteria for potentially inappropriate medication use in older adults since the 1990s [24]. Opioids may also pose a falls risk in older adults [25], yet the opioid deprescribing movement has only recently expanded [26, 27]. Our data show that opioid use decreased to a lesser degree than that of benzodiazepines. Future research could investigate if a decrease in opioid use occurred in seniors subsequent to the release of recent opioid guidelines in Canada [26] and the USA [27].

We also observed an apparent shift in gastrointestinal drug prescribing. Here, H2RA use decreased in tandem with an

increase in PPI use, which is concerning since PPI use may increase fracture risk by impairing calcium absorption, though evidence remains controversial [28, 29]. Although data emerged over the course of the last 20 years suggesting superiority of PPIs over H2RAs in the treatment of select indications [30], we believe the switch observed in our study may also relate to our inability to capture over-the-counter medication use. Our data were collected through the billing of the provincial public drug program, allowing only the recording of prescription medications. H2RAs, including ranitidine, famotidine, and cimetidine, have been available over-the-counter in Canada since 1997 [31], whereas all PPIs were prescription-only until 2014 [32]. We also noted trends in hormone therapy use among women, with sharp decline in use after 2002 that is likely due to results from the Women's Health Initiative study, published in 2002, which provided evidence that estrogen-based therapies increased the risk of stroke and blood clots among postmenopausal women [33]. Moreover, in 2002, clinical practice guidelines in Canada changed to support bisphosphonate treatment as first-line therapy for osteoporosis and demoted hormone therapies to second-line treatment [34].

Our study was not without limitations. First, we were limited to publicly funded pharmacy claims, preventing us from assessing drugs processed out-of-pocket, in-hospital, or purchased over-the-counter. We also were not able to capture claims through private drug plans. It is estimated that 15% to 20% of seniors in Ontario had at least one claim through private drug coverage from 2000 to 2005 [35]. However, approximately 95% of seniors had a publicly funded drug claim, and private drug plans are generally only utilized when the drug dispensed is not listed on the Ontario provincial formulary [35, 36]. We also identified 15,211 patients initiating a drug other than an oral bisphosphonate as their first osteoporosis medication (half starting denosumab); this may be attributed to the aforementioned sources of exposure misclassification of first osteoporosis drug, such as private drug coverage claims or missing data on bisphosphonate use prior to age 65. This is hypothesized given that initial treatment with or intolerance to oral bisphosphonate is required for coverage of denosumab since it was added to Ontario public drug formulary in 2012, and over the duration of this study [2, 3]. Better understanding of use of private drug coverage before and after age 65 is of interest. Second, we were unable to assess emergency department visits until 2001, the year the database housing this information was established [37]. In addition, diagnostic codes used to characterize patient comorbidities may have different sensitivity and specificity over time, particularly regarding modifications from the International Statistical Classification of Diseases and Related Health Problems, Canada (ICD-CA) 9th to 10th editions in Ontario in 2002 [38].

Our study has notable strengths. Prior studies describing Canadian bisphosphonate prescribing have only included data until 2009 and simply compared the type of drug dispensed [1]. Our study integrates data obtained through to March of 2016, encompassing a full 20 years, and considers patient characteristics over time and the introduction of new bisphosphonate formulations. Finally, this study provides evidence of sex-specific differences in patient characteristics over time, outlining important differences in time trends between men and women.

In summary, oral bisphosphonates remain the primary treatment of osteoporosis in Ontario. Our data demonstrate significant time trends in the type of bisphosphonate initiated as well as factors affecting fracture risk (e.g., benzodiazepine use) and mortality (e.g., patient comorbidities). Because of these time trends, patients may not be comparable if the study dates span eras of major changes in practice guidelines, drug policy, or healthcare delivery. Even if analytic techniques to account for potential confounding variables are employed, healthcare administrative data may not contain sufficient information to eliminate the possibility of residual confounding between patients initiating therapy over different periods of time [7–9]. Therefore, careful consideration must be given to time trends when designing studies that examine bisphosphonate drug safety and effectiveness, as well as any examination of fracture risk among this population.

Funding information This research was supported, in part, by Canadian Institutes of Health Research Drug Safety and Effectiveness Cross-Disciplinary Training Program Stream 1 Trainee Awards to Kaleen Hayes and Joann Ban. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOHLTC is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institutes of Health Information (CIHI). However, the analyses, conclusions, opinions, and statements expressed in the material are those of the author(s) and not necessarily those of CIHI. We thank IMS Brogan Inc. for use of their Drug Information Database. All analyses were completed at the ICES University of Toronto site, supported by the Leslie Dan Faculty of Pharmacy.

Compliance with ethical standards

This study was approved by the Research Ethics Boards at Sunnybrook Health Sciences Centre in Toronto and the University of Toronto.

Conflicts of interest None.

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