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ORIGINAL ARTICLE

Denosumab utilization among older adults in Ontario: patient characteristics, persistence with therapy, and return to therapy after an extended gap

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Abstract

Summary We studied 46,797 older adults who initiated denosumab in Ontario, Canada. Patient characteristics remained relatively stable over time and aligned with public reimbursement restrictions. Almost half of patients persisted with therapy for at least 3 years. Fifty-nine percent of patients who discontinued denosumab returned to treatment within 3.6 years.

Introduction The purpose of this study was to describe the characteristics of patients who initiated denosumab and estimate persistence with therapy.

Methods We identified older adults (aged ≥ 66 years) in Ontario who initiated denosumab between 2012/02 and 2015/03 and followed them to 2016/03. Patient characteristics were summarized using medical and pharmacy claims in the year before starting denosumab and osteoporosis drug use considered since 1996/10. Persistence with denosumab and return after discontinuation (> 90-day gap) were estimated using Kaplan–Meier curves. Analyses were stratified by community and long-term care (LTC) residence.

Results We identified 46,797 patients (monthly mean = 1263, SD = 187); 97% female, 13% LTC. Community-dwelling patients had a higher prevalence of bone mineral density testing (62% vs. 5%), yet were younger (mean age 78.5 vs. 86.6 years) and had lower prevalence of hip fractures (3% vs. 10%) compared to LTC patients. Eighty-two percent of patients had used osteoporosis medications in the past; 99% of whom took an oral bisphosphonate. Persistence was similar between community-dwelling and LTC patients: 59% persisted ≥ 2 years, 48% ≥ 3 years, and 38% ≥ 4 years, yet a larger proportion of LTC patients returned to denosumab after discontinuation (76% vs. 57%).

Conclusions Denosumab utilization is increasing at a steady rate in Ontario. However, persistence remains a concern given the highly reversible pharmacokinetic profile of denosumab that results in a rapid increased fracture risk following discontinuation. Over 80% of patients had a history of oral bisphosphonate therapy, which may persist in bone despite discontinuing denosumab. Consequently, better understanding of denosumab safety and effectiveness among real-world users is important.

Keywords Denosumab · Health services research · Medication adherence · Osteoporosis · Persistence

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Introduction

Denosumab is a fully human monoclonal antibody with high affinity and specificity for receptor activator of nuclear factor kappa-B ligands (RANKLs). Denosumab works by inhibiting osteoclast formation, function, and survival, thus reducing bone resorption and turnover. A single 60 mg injection decreases bone turnover markers and increases bone mineral density (BMD) [1–3]. Injections every 6 months increase BMD by 3–9% within 24 months and reduce fracture risk at the spine, hip, and other sites [2–4]. Compared to weekly alendronate or monthly risedronate, denosumab results in greater increases in BMD at the spine, hip, and radius.

However, denosumab has a reversible onset of action. Bone turnover markers return to baseline at 9 months following injection [1], and discontinuation of denosumab results in a steady decline in BMD back to pre-treatment levels by 24 months following discontinuation [3]. Due to the highly reversible pharmacokinetic profile of denosumab [1, 3], persistence is an important consideration for effective osteoporosis pharmacotherapy. Patients who are non-persistent are at increased risk of fracture [5–7].

Denosumab was approved by Health Canada for postmenopausal osteoporosis in August 2010 [8] and added to the Ontario Drug Benefit (ODB) formulary for public reimbursement in February 2012 [9]. The ODB restricted coverage to postmenopausal women at high risk of fracture and those with a hypersensitivity to bisphosphonates following their use. Despite coverage restrictions, rapid uptake was noted with 16,736 patients initiating denosumab within 15 months of public availability [9]. Prior non-experimental studies report persistence with denosumab between 56 and 95% at 12 months of initiation and 35 to 86% at 24 months [10–22]. Part of the challenge in comparing estimates of persistence across studies relates to inconsistent definitions in the permissible gap length between prescriptions, which denotes drug discontinuation [23]. The permissible gap in prior studies range between 30 and 90 days, with no standard or rationale provided for the choice of gap length.

Our study aimed to (1) describe the characteristics of older adults who initiated denosumab in Ontario, (2) estimate persistence with therapy using a pharmacologic definition of discontinuation, and (3) estimate return to therapy after discontinuation. Given the known differences in the characteristics and clinical care of older adults who reside in the community versus long-term care (LTC), we considered patients who resided in the community separately from patients who resided in LTC. To our knowledge, no prior study has described denosumab treatment in LTC. We hypothesized that persistence with therapy would be higher among patients in LTC due to more careful patient monitoring.

Methods

We used Ontario healthcare administrative claims (medical and pharmacy) to identify and describe older adults who initiated denosumab (60 mg/mL injection; drug identification number 02343541) from February 29, 2012 (first date of public availability) to March 31, 2015. Ontario medical and pharmacy claims data are widely used for the purposes of research and have been demonstrated to be of high quality [24–26]. These datasets were linked using unique encoded identifiers and analyzed at ICES. Use of these data was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. We included people aged 66 years or more at treatment initiation to ensure a minimum of 1 year of pharmacy claims history. The first date of denosumab dispensation over the entire study period was considered the index date. Patients who were diagnosed with health conditions (celiac disease, Cushing's syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasms, organ transplant, osteomalacia, osteopetrosis, Paget's disease, or renal impairment) or drugs (estrogen therapy among men or non-osteoporosis bisphosphonates such as clodronate and pamidronate) that impact bone integrity within 1 year prior of starting denosumab were excluded. Despite the fact that denosumab indicated for cancer is marketed under a different name and dose (120 mg/1.7 mL; drug identification number 02368153), frequent dispensing of the 60 mg/mL injection indicated for osteoporosis may suggest off-label use of denosumab for indications other than osteoporosis, such as bone metastases [8, 27]. Consequently, patients who received more than 3 denosumab claims within a year of treatment initiation were also excluded. Finally, patients with data coding errors, defined as a death date prior to treatment initiation or missing sex, were excluded.

Patient characteristics

We identified patient age, sex, and region of residence at denosumab initiation and emergency department visits, hospitalizations (0, 1, or ≥ 2), outpatient visits (mean number), BMD testing, osteoporosis diagnosis, hip fracture, and comorbid drug use (i.e., drugs that may impact BMD or falls risk [28]) within 1 year of starting denosumab. We also summarized prior osteoporosis drug use since October 1, 1996 (the date the first eligible osteoporosis drug, etidronate, was added to the ODB formulary) [29], defined as a binary variable (yes/no) and summarized by (1) osteoporosis drug type (oral bisphosphonates, nasal calcitonin, raloxifene, and zoledronic acid) and (2) number of years of prior use. The dispensation of any osteoporosis drug within each year prior to denosumab initiation defined osteoporosis drug use in that year.

Persistence with therapy

The number of doses and length of time on denosumab therapy were defined based on denosumab dispensation dates. Since denosumab injections are dosed once every 6 months, we imputed 183 days (the average number of days in any 6-month calendar period) as the length of therapy for each dispensation. Consequently, each patient persisted with denosumab therapy for a minimum of 183 days from the first date of denosumab dispensation. Patients who did not receive a new denosumab claim within 9 months (183 + 90 = 273 days) were considered to have discontinued. This is consistent with prior studies that have demonstrated a return of

bone turnover markers (i.e., urinary N-telopeptide markers) to baseline 9 months after injection [1]. Discontinuation date was defined by date of last dispensation + 183 days. Persistence was defined as the total length of time a patient continued denosumab therapy, starting from the first date of denosumab dispensation (treatment initiation or index date) until treatment discontinuation [23]. We then examined the length of time to return to denosumab therapy among patients who discontinued treatment.

Statistical analysis

We described patient characteristics overall and by fiscal year. Given that formulary access for denosumab began on February 29, 2012, baseline characteristics for patients who initiated denosumab in February and March 2012 were included in the 2012/13 fiscal year. The Kaplan–Meier method was used to estimate the proportion of patients who continued therapy at each 183-day interval and summarized at 1, 2, 3, and 4 years after treatment initiation. Patients were censored at the first date of death, discontinuation, or March 31, 2016 (the last date of available data). We then used the Kaplan–Meier method to estimate the time to return to denosumab among patients who discontinued therapy. All statistical analyses were stratified by community and LTC residence and conducted using SAS software, version 7.1 (SAS Institute Inc., Cary, North Carolina) [30]. Given the recent movement away from reporting *p* values that are largely based on statistical power [31, 32] and that we were dealing with a large sample of patients, no statistical tests were used to compare the characteristics between patients who resided in the community and in LTC.

Results

Patient characteristics

Of 51,936 patients aged 66 years or older who initiated denosumab as of 2015/03, 4474 were excluded based on comorbidity or other drug use, 635 for non-osteoporosis denosumab use, and 30 for database coding errors. Therefore, a total of 46,797 (90.1%) were eligible for inclusion (40,895 community, 5902 LTC). The number of patients who initiated denosumab therapy increased steadily over time with a mean of 1263 (SD = 187.1, min = 834, max = 1621) new patients each month. Ninety-seven percent of patients were female, and 87% resided in the community (Table 1). Compared to LTC patients, community-dwelling patients were younger (mean age = 78.5 years, SD = 7.3 community; mean age = 86.6 years, SD = 6.6 LTC); more commonly resided in urban regions (80.4% community, 69.6% LTC); had a higher prevalence of BMD testing (62.1% community, 4.7% LTC); and had a lower proportion of emergency department visits (39.1% community, 55.3% LTC), hospitalizations (15.5% community, 30.9% LTC), and outpatient visits (mean number = 21.4 visits, SD = 20.6 community; mean number = 30.9 visits, SD = 29.7 LTC). In addition, a lower proportion of community-dwelling patients took medications that increase the risk of falls: opioids (30.3% community, 42.9% LTC) and benzodiazepines (16.6% community, 21.5% LTC). With few exceptions, such as a decline in the use of proton pump inhibitors among LTC patients (52.1 to 45.8%), patient characteristics remained relatively stable over time (data not shown).

History of osteoporosis therapy

Fifty-nine percent of patients (57.8% community, 60.4% LTC) were treated with other osteoporosis medications in the year prior to initiating denosumab. This increased to 82% (83.1% community, 78.0% LTC) when looking back as far as October 1996, Table 2. Of the 38,599 (82.5%) patients treated with an osteoporosis drug before starting denosumab therapy, 42.1% had 6 or more years of prior use, 33.4% had 3 to 5 years of prior use, and 24.5% had 1 to 2 years of prior use.

Persistence with therapy

Persistence with denosumab was similar between community-dwelling and LTC patients, Fig. 1. Overall, 74.8% persisted ≥ 1 year, 59.0% persisted ≥ 2 years, 48.1% persisted for ≥ 3 years, and 37.7% persisted ≥ 4 years. A higher proportion of LTC patients returned to denosumab therapy following discontinuation compared to community-dwelling patients (76.3% LTC vs. 57.0% community), Fig. 2. In addition, LTC patients returned to therapy more quickly: 42.9% returned within 1 year (41.0% community, 63.1% LTC), 52.5% within 2 years (50.8% community, 71.3% LTC), 56.6% within 3 years (55.0% community, 73.7% LTC), and 58.5% within 3.6 years (57.0% community, 76.3% LTC).

Discussion

We followed more than 46,000 patients who initiated denosumab therapy since February 2012, using a well-validated healthcare administrative database that captured all denosumab claims dispensed through the public drug plan in Ontario [26, 34]. This reflects an estimated annual rate of 1% of older female adults initiating denosumab in Ontario based on the population size of women aged 65 or more years [35]. In contrast to an American study that identified an increase in the use of newly marketed injectable osteoporosis drugs among patients with lower fracture risk over time [36], we noted little change in the characteristics of patients who initiated denosumab over time. However, little change in our study

Table 1 Characteristics of patients who initiated denosumab in Ontario by community and long-term care setting, 2012/02 to 2015/03, $N = 46,797$

	Community-dwelling, $N = 40,895$	Long-term care, $N = 5902$
Age, mean ± SD	78.5 ± 7.3	86.6 ± 6.6
Female, %	96.7	98.1
Region of residence[a], %		
Urban	80.4	69.6
Non-major urban	16.4	25.1
Rural	3.2	5.3
Health services use in past year[b]		
Emergency department visits, %	39.1	55.3
In-patient hospitalization, %		
1	11.6	23.6
2+	3.9	7.3
Outpatient Visits, mean number ± SD	21.4 ± 20.6	30.9 ± 29.7
Osteoporosis related[b], %		
Bone mineral density test	62.1	4.7
Osteoporosis diagnosis	56.0	9.7
Hip fracture	2.8	9.8
Medications[b,c], %		
Anticancer[d]	1.8	1.2
Antihypertensives	64.3	69.2
Antiarrhythmics	3.2	6.6
Anticoagulants	8.5	17.6
Antiplatelets	2.5	4.2
Nitrates	3.2	9.3
Statins	45.9	39.6
Oral antidiabetics	9.8	12.5
Insulins	1.6	4.3
Antihypothyroidism	21.6	27.3
Proton pump inhibitors	36.7	48.6
Hormone therapy	4.2	1.7
Oral corticosteroids	9.4	9.3
Non-steroidal anti-inflammatory drugs	13.1	9.2
Opioids	30.3	42.9
Anticonvulsants	6.0	11.8
Antiparkinson drugs	2.2	7.6
Psychiatric disorders		
Antipsychotics	3.4	33.8
Alzheimer's or other dementias	4.8	39.1
Benzodiazepines	16.6	21.5
SNRIs	4.0	9.3
SSRIs	11.0	39.3
Tricyclic antidepressants	4.5	4.3
Respiratory drugs	18.5	22.7
Anticholinergics	6.6	11.4
Bronchodilators	13.5	18.7

SD standard deviation, *SNRIs* serotonin and norepinephrine reuptake inhibitors, *SSRIs* selective serotonin reuptake inhibitors

[a] Proportions adjusted for missing regional data (< 1%)

[b] 1-year look-back period from denosumab initiation

[c] ≥ 2 prescriptions

[d] Included antiandrogens (men only), antiestrogens (women only), aromatase inhibitors (women only), and gonadotropin-releasing hormone analogues

is logical given the highly restricted public drug reimbursement policy for denosumab in Ontario. To our knowledge, our study is the largest to examine denosumab and the first to consider patients residing in LTC. As expected, LTC patients were older and more frail in comparison to community-dwelling patients [37]. However, LTC patients had fewer

Table 2 Proportion of patients with osteoporosis drug use by community and long-term care setting, $N = 46{,}797$

Setting	Community, $N = 40{,}895$		Long-term care, $N = 5902$	
Look-back period	1 year	Since 1996/10	1 year	Since 1996/10
Prior use (any)[a], %	57.8	83.1	60.4	78.0
Oral bisphosphonate	56.1	82.2	59.8	77.7
Alendronate	20.0	42.7	17.9	37.9
Etidronate	1.6	35.7	1.2	41.3
Risedronate	36.3	57.1	43.8	56.6
Other[b, c]	3.0	8.9	0.9	3.9
Raloxifene	2.6	7.6	0.7	3.3
Zoledronic acid	0.4	1.1	0.2	0.5

[a] Patients may have used more than one type of osteoporosis drug

[b] Teriparatide is not a benefit under the Ontario Drug Benefit Program

[c] Calcitonin was removed from the market in October 1, 2013 and is not shown [33]; < 0.4% of patients had prior calcitonin use

physician-claimed diagnoses of osteoporosis and fewer BMD tests within the year prior to starting denosumab. A validation study in Ontario found that osteoporosis diagnosis identified using physician claims is poor, yet BMD testing is accurate [26]. Because LTC patients tend to be older, more frail, and at a higher risk of falls and fractures, LTC patients may have received a clinical diagnosis of osteoporosis (as opposed to a diagnostic one based on BMD testing) and were thus initiated on denosumab [37]. This is supported by the fact that 78% of patients who started denosumab in LTC were previously treated for osteoporosis and, thus, also likely had BMD testing, yet more than a year before the initiation of denosumab.

LTC patients had similar rates of persistence to community-dwelling patients, which is interesting and inconsistent with our hypothesis of longer persistence considering that LTC residents typically have more medical and personal support available to them, such as automated drug refills and assistance with the administration of medications [38]. Overall, we found that 75% of patients persisted with denosumab for at least 1 year, and 59% persisted for at least 2 years; estimates that are comparable to persistence rates identified in smaller observational studies (56–95% at 1 year, 35–86% at 2 years) [10–22]. However, these studies only followed patients for up to 2 years. To our knowledge, our study is the first to consider persistence for longer than 2 years, finding that 48% of patients persisted for at least 3 years and 38% persisted for 4 or more years.

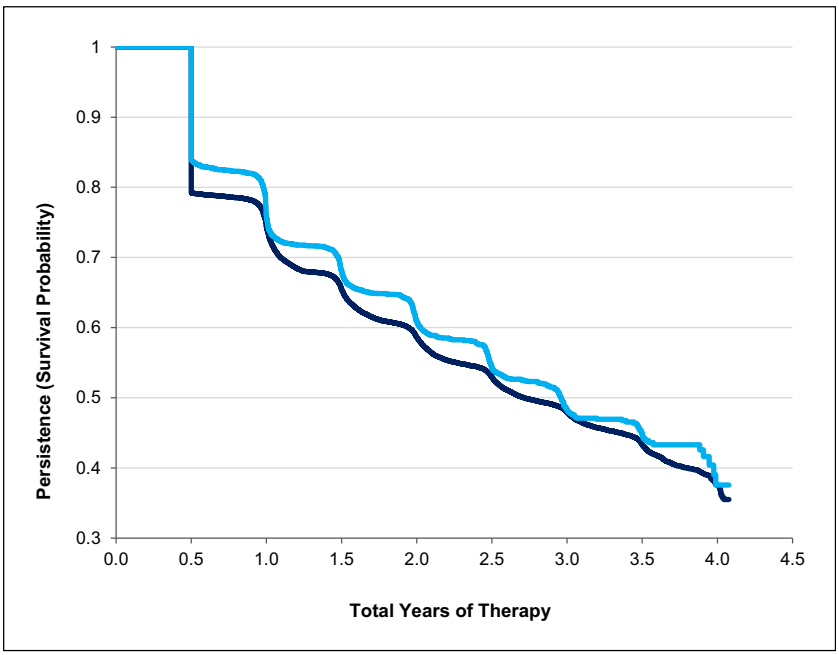

Fig. 1 Kaplan–Meier estimates of persistence among patients who initiated denosumab by community (dark blue line, $N = 40{,}895$) and long-term care (light blue line, $N = 5902$) setting

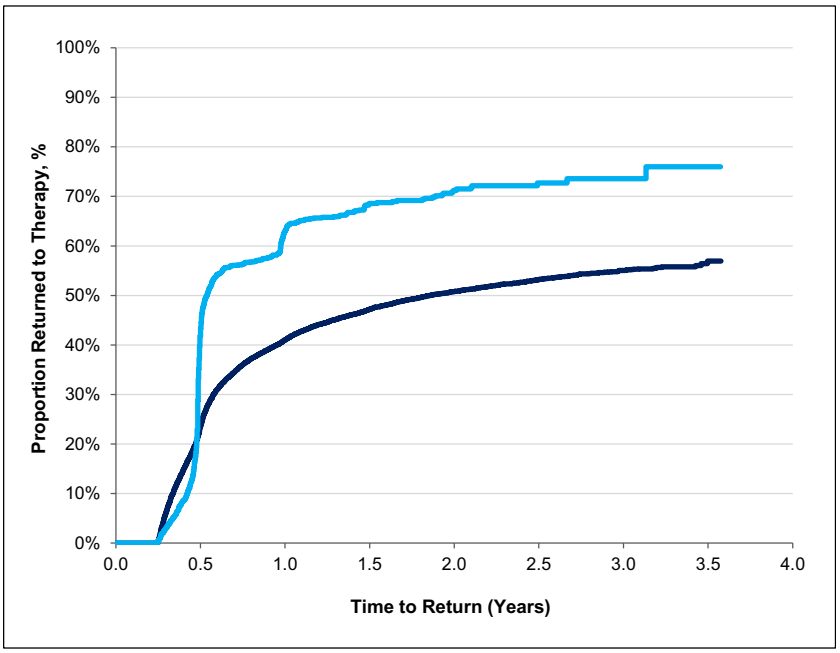

Fig. 2 Kaplan–Meier estimates of the time to return to denosumab therapy in years following treatment discontinuation by community (dark blue line, $N = 18{,}678$) and long-term care (light blue line, $N = 1949$) setting

It is estimated that a quarter of Canadians who were taking denosumab in 2013 were enrolled in a patient support program, ProVital [11]. Patient support programs provide services that can help patients better manage their diseases (e.g., education pamphlets on disease management, medication counseling, injection reminder calls, therapeutic monitoring). Despite this, persistence with denosumab decreased over time. Just under half of Ontario patients persisted with therapy for 3 years. Our declining rates may partly relate to delays in subsequent injections, since denosumab requires semi-annual visits to a healthcare provider for administration. Indeed, return to denosumab after our defined treatment gap of 90 days (183 + 90, or about 9 months from last dose) was rapid, with 24% (community) to 43% (LTC) of patients receiving another dose of denosumab within 6 months following discontinuation. This increased to 41% and 63% at 1 year and 57 to 76% over the study period up to 3.6 years of follow-up. Quicker return among LTC patients may reflect higher commitment to denosumab due to closer surveillance by medical staff. With no prior research on persistence with denosumab in LTC, our results provide some evidence of the benefits of supportive care and encourage further consideration of institutional factors and their effect on treatment persistence. Nonetheless, unlike oral bisphosphonates that persist in bone, denosumab has a rapid offset of action with BMD declines of 5.3–6.6% at the lumbar spine and hip within 12 months of discontinuation [39] and returns to pre-treatment levels within 24 months of discontinuation [3]. Although the pivotal phase III FREEDOM trial found little to no increase in fracture risk following 24 months of discontinuation of denosumab therapy [5], more recent post hoc analyses identify an increase in the incidence of multiple vertebral fractures [7]. The highly reversible nature of denosumab, and emerging evidence of excess fracture risk [7, 40, 41], make ongoing therapy or switch to another osteoporosis drug after stopping an important consideration [42, 43]. Our study considered persistence through to March 2016, a timeline before recent evidence of increased fracture risk became available. Consequently, some patients in our study may have started a physician-directed drug holiday before the importance of continued therapy or switch to another osteoporosis medication became known.

Interestingly, patients in the post hoc analyses had little to no prior oral bisphosphonate use, and none in the year prior to starting denosumab [7]. This contrasts with over 80% of patients in our study who had prior oral bisphosphonate use. Greater historical exposure to bisphosphonates may signify less immediate need for alternative osteoporosis therapies after denosumab is stopped, since bisphosphonates are retained in the bone long after discontinuation of bisphosphonate therapy [40, 42, 44]. However, how much bisphosphonate exposure is required for a lasting protective effect upon denosumab discontinuation and how long of a drug holiday is appropriate before reinitiation of denosumab or another osteoporosis therapy is unclear and of interest for future research.

A few study limitations are worth noting. First, we were limited to data among residents aged 66 or more years, potentially underestimating the number of Ontarians who initiated denosumab therapy. However, denosumab is targeted for the treatment of, and not prevention of, osteoporosis, and thus, we anticipate that few patients younger than 65 would have been treated for osteoporosis with denosumab and thus been missed in our analysis. Our second limitation is in defining community or LTC residence only at the time of the first denosumab claim. Some patients may have switched between community

and LTC residence during our study. However, less than 3% of patients switched between community and LTC residence during our study, making the impact of misclassification likely small. Third, due to an error in dataset creation, we were unable to consider fractures other than fractures of the hip within 1 year of initiating denosumab therapy. Finally, as of February 2018, reimbursement criteria for denosumab have broadened to include men, patients who have failed any available osteoporosis therapy (i.e., no longer restricted to oral bisphosphonates), and a more lenient definition of high fracture risk. We therefore anticipate that more men and women will be exposed to denosumab in the future. Future research that considers denosumab and oral bisphosphonate exposure patterns, including switching between treatment options, reasons for discontinuation, switching or restarting therapy, and the subsequent impacts on real-world safety and effectiveness are important to optimize treatment adherence and patient outcomes.

In summary, denosumab use is increasing among older adults in Ontario at a rate of 1% of female seniors annually. Patient characteristics remained relatively stable over time and may point to the success of strict reimbursement criteria that limits use of denosumab to patients at high fracture risk. Fifty-nine percent of patients persisted with denosumab therapy for at least 2 years, and nearly 40% for at least 4 years. Recent evidence from extension trials identifies potentially rapid and harmful effects on bone following the discontinuation of denosumab. Given that older adults in Ontario who initiate denosumab are at high risk of fracture, rates of discontinuation are concerning. It is interesting to note that over 80% of patients in our study were exposed to oral bisphosphonate therapy prior to initiating denosumab. Oral bisphosphonates are known to persist in bone with residual effectiveness after discontinuation and thus may also reduce fracture risk following the discontinuation of denosumab. Further research that considers the impact of treatment patterns on the safety and effectiveness of denosumab, including prior bisphosphonate use and switches between treatment options, is important to inform clinical practice.

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Compliance with ethical standards

Conflicts of interest None.

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