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Research Article

On-time denosumab dosing recovered rapidly during the COVID-19 pandemic, yet remains suboptimal

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Abstract

Timely administration of denosumab every 6 mo is critical in osteoporosis treatment to avoid multiple vertebral fracture risk upon denosumab discontinuation or delay. This study aimed to estimate the immediate and prolonged impact of the COVID-19 pandemic on the timing of denosumab doses. We identified older adults (≥66 yr) residing in the community who were due to receive denosumab between January 2016 and December 2020 using Ontario Drug Benefit data. We completed an interrupted time-series analysis to estimate the impact of the COVID-19 pandemic (March 2020) on the monthly proportion of on-time denosumab doses (183 +/−30 d). Analyses were stratified by user type: patients due for their second dose (novice users), third or fourth dose (intermediate users), or ≥5th dose (established users). In additional analyses, we considered patients living in nursing homes, switching to other osteoporosis drugs, and reported trends until February 2022. We studied 148 554 patients (90.9% female, mean [SD] age 79.6 [8.0] yr) receiving 648 221 denosumab doses. The average pre-pandemic proportion of on-time therapy was steady in the community, yet differed by user type: 64.9% novice users, 72.3% intermediate users, and 78.0% established users. We identified an immediate overall decline in the proportion of on-time doses across all user types at the start of the pandemic: −17.8% (95% CI, −19.6, −16.0). In nursing homes, the pre-pandemic proportion of on-time therapy was similar across user types (average 83.5%), with a small decline at the start of the pandemic: −3.2% (95% CI, −5.0, −1.2). On-time therapy returned to pre-pandemic levels by October 2020 and was not impacted by therapy switching. Although on-time dosing remains stable as of February 2022, approximately one-fourth of patients in the community do not receive denosumab on-time. In conclusion, although pandemic disruptions to denosumab dosing were temporary, levels of on-time therapy remain suboptimal.

Keywords: osteoporosis, antiresorptives, fracture prevention, general population studies, health services research

Lay Summary

This study investigated the impact of the COVID-19 pandemic on timely administration of denosumab. Denosumab is an injectable medication used to treat osteoporosis (a disease characterized by decreased bone strength) and must be administered on time every 6 mo to avoid increased risk of spine fracture. We identified immediate and significant delays in denosumab therapy early during the COVID-19 pandemic, particularly among adults living in the community. Although on-time denosumab therapy returned to pre-pandemic levels by October 2020, approximately 1 in 4 patients still do not receive denosumab within the recommended timeframe. These findings raise concerns about increased fracture risk and highlight the need to identify barriers and solutions to promote on-time denosumab therapy.

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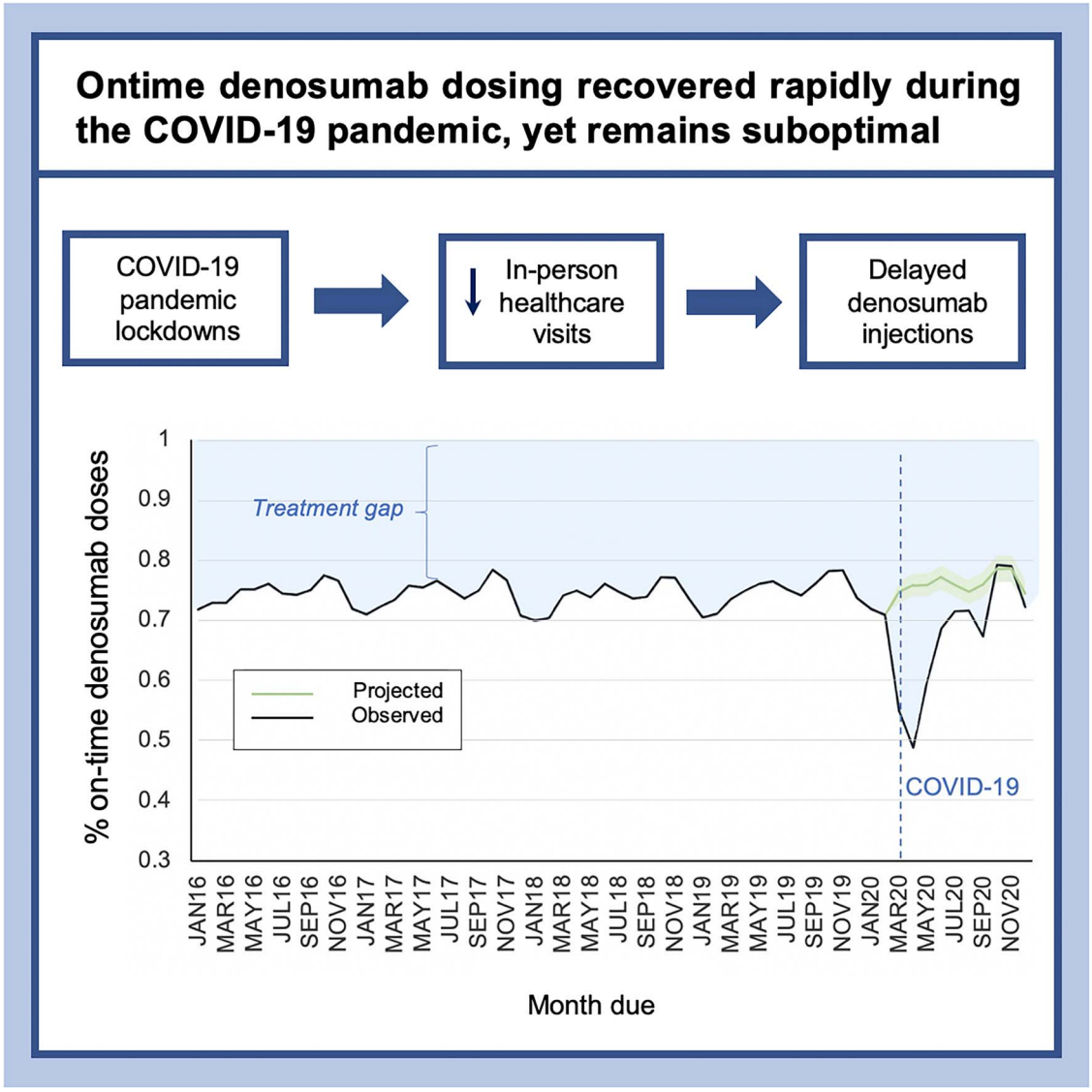
Graphical Abstract



Introduction

Denosumab is an effective osteoporosis therapy that is administered as a semi-annual subcutaneous injection. Although denosumab reduces osteoporotic fracture risk during therapy,[1] delayed injections and denosumab discontinuation have been associated with increased risk of multiple vertebral fractures as early as 2 mo after a missed injection.[2–4] Importantly, longer use of denosumab is associated with greater bone loss and an increased number of vertebral fractures following denosumab discontinuation.[5–7] Vertebral fractures, and particularly multiple vertebral fractures, are associated with chronic back pain and increased risk of morbidity and mortality.[8,9] Thus, it is critically important for patients to receive denosumab injections on time every 6 mo to avoid excess fracture risk. If denosumab is discontinued or delayed longer than 1 mo beyond the 6-mo due date, it is recommended that patients transition to an alternate osteoporosis therapy to reduce the risk of vertebral fractures.[10,11]

The coronavirus disease 2019 (COVID-19) pandemic led to worldwide disruptions in the delivery of healthcare services,[12–14] raising concerns about delays in denosumab administration. For example, in-office primary care visits decreased 80% in Ontario during March 2020 and remained low through to the end of the calendar year.[12] Even when combined with virtual medical assessments, primary care visits decreased by more than 20% among patients aged 65 and older.[12] In Ontario, denosumab has historically been administered in the prescribing physician's clinic. Thus, the transition to virtual care and overall decline in medical assessments may have disrupted timing of denosumab injections. Indeed, reduced access to medical facilities and fear of COVID-19 infection have been reported internationally as reasons for denosumab delays.[15,16]

We conducted a population-based ecological study that employed interrupted time-series analysis to estimate the immediate and extended impact of the COVID-19 pandemic on the proportion of older adults who receive on-time denosumab therapy. We hypothesized an immediate decrease in on-time denosumab doses at the start of the pandemic that would not recover by the end of 2020. We were also interested

in comparing results by the length of prior denosumab exposure. We hypothesized that patients with a longer history of denosumab use would have a consistently higher proportion of on-time doses that would be less impacted by the pandemic.

Materials and methods

This study followed methodological and reporting guidelines for interrupted time-series analyses,[17] adapted from the Strengthening and Reporting of Observational Studies in Epidemiology initiative.[18]

Study design, population, and data sources

We completed a population-based ecological (interrupted time series) study that utilized universal healthcare administrative data for all Ontario residents aged 65 yr or more. Denosumab is publicly funded under the Ontario Drug Benefits (ODB) plan for residents aged ≥65 yr at high risk of fracture who have a contraindication or inadequate response to oral bisphosphonates.[19] We first used the ODB database to identify all residents aged 65 yr or older who initiated denosumab (*Prolia*® 60 mg subcutaneous injection, drug identification number = 2342541) between February 1, 2012 (first month available) and July 31, 2021 (last date available at the time of dataset creation).[10] Patients' age, sex, and death date were identified through the Registered Persons Database, and residence in the community or nursing home (known as long-term care in Ontario) was identified using ODB dispensation flags and the Continuing Care Reporting System database. Malignancy-related exclusions were identified using data from the Ontario Cancer Registry (OCR). Datasets were linked using unique encoded identifiers and analyzed at ICES (www.ices.on.ca). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

From our cohort of denosumab users, we identified patients who received at least one denosumab dose between July 2015 and July 2020 as eligible. Patients were due for their next denosumab dose 6 mo (183 d) later, between January 2016 and December 2020. Restricting our baseline period to begin in 2016 avoided capturing potential irregularities in early uptake of denosumab[20,21] while satisfying modelling guidelines that recommend at least 50 pre-intervention timepoints.[22] The study period was restricted to the end of 2020 to capture the impact of the first wave of the pandemic without co-intervention from secondary lockdowns or COVID-19 vaccination in early 2021. We excluded patients with database errors (death date before first denosumab dose or missing age), and those younger than 66 yr to permit a minimum 1-yr lookback for prior denosumab use (ODB data are limited to dispensation data for patients aged ≥65 yr). We also excluded patients with evidence of malignancy (OCR) or suspected malignancy (4 or more denosumab doses within 365 d, dispensation of non-osteoporosis bisphosphonate or denosumab). History of denosumab use since its availability in February 2012 was determined at each due date and categorized into 3 user groups: patients due for their 2nd dose (novice users), 3rd or 4th dose (intermediate users), or ≥5th dose (established users).

Outcome

The primary outcome of interest was the monthly proportion of patients residing in the community who received an on-time denosumab dose. The number of patients due for a denosumab dose on any given day was based on the number of patients who received a denosumab dose 6 mo (183 d) earlier (reference dose; Figure 1). We calculated the average proportion of patients who received their denosumab dose on time (within +/−30 d of the due date) for each calendar month. Patients were only eligible to be included in the monthly proportion of on-time doses if they survived until 183 + 30 d after their prior dose and remained community-dwelling. This was to ensure only surviving patients who resided in the community were considered. Our on-time definition was based on current guidelines that recommend denosumab not be delayed more than 1 mo beyond the recommended due date.[11]

Statistical analysis

We summarized patient characteristics at date of first reference denosumab dose using descriptive statistics, overall, and by residence (community or nursing home). We then plotted the monthly proportion of on-time denosumab therapy to describe pre-pandemic trends by residence and denosumab history. Next, we conducted an interrupted time-series analysis using autoregressive integrated moving average (ARIMA) modeling. ARIMA models are commonly used in healthcare research to identify the impact of an intervention on an outcome over time, particularly when time-series data are non-linear or seasonal. Unlike segmented regression models, ARIMA models inherently account for autocorrelation, non-stationarity, and seasonality in data. We employed ARIMA modeling in this analysis as we predicted a strong seasonal pattern in timeliness of denosumab dispensations and could not rule out non-linear trends.

The intervention of interest was the beginning of the COVID-19 pandemic (March 2020) and our outcome of interest was the proportion of on-time denosumab doses in each calendar month. We included 50 pre-intervention timepoints (January 2016 to February 2020), satisfying recommendations for ARIMA modeling.[22] The analysis was conducted at the level of individual due dates, and thus each patient could contribute multiple due dates to the analysis.

ARIMA models were built using Box-Jenkins methodology and accounted for non-stationarity and seasonality.[23] Autoregressive and moving average parameters were selected to minimize peaks in autocorrelation function and partial autocorrelation function plots, and diagnostic checks of normality and autocorrelation of residuals were performed. Where multiple models satisfied diagnostic criteria, the model with the lowest Akaike Information Criterion was selected. A priori, we hypothesized an immediate drop in on-time denosumab therapy at the start of the pandemic that would not recover by December 2020. However, preliminary analyses identified an abrupt yet temporary impact, and thus the intervention was modeled using a 2-mo pulse transfer function (March and April).[23–26]

In secondary analyses, we examined results stratified by denosumab history, estimated the proportion of patients that did not return to denosumab therapy within 1 yr of their prior dose, and repeated analyses for doses due among nursing home residents. In sensitivity analyses, we expanded the definition of on-time dosing to +/−60 d and incorporated

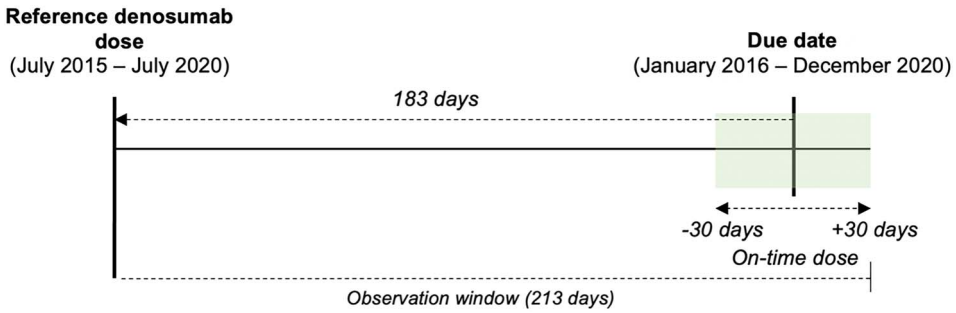


Figure 1. Method to define denosumab due date and on-time therapy. Patients were considered to have an on-time dose if their next denosumab dose after the reference dose occurred within +/−30 d (shaded interval) of the 183-d due date.

Table 1. Patient characteristics at first denosumab dose between July 2015 and July 2020, *N* = 148 554.

Patient Characteristics	Community (*n* = 125 963)	Nursing home (*n* = 22 591)	Total (*n* = 148 554)
Female, %	91.3	88.9	90.9
Age, mean (SD)	78.3 (7.5)	86.3 (7.2)	79.6 (8.0)
Number of prior denosumab doses, mean (SD)	0.9 (1.8)	0.7 (1.6)	0.9 (1.7)
Denosumab user group,[a] %			
Novice users (Due for second dose)	72.3	76.1	72.9
Intermediate users (Due for third or fourth dose)	11.8	10.8	11.7
Established users (Due for ≥5th dose)	15.8	13.1	15.4
Oral bisphosphonate history,[b] %, overall	38.8	43.7	39.5
Oral bisphosphonate history,[b] %, by denosumab user group			
Novice users (Due for second dose)	49.3	52.2	49.7
Intermediate users (Due for third or fourth dose)	25.0	34.2	26.3
Established users (Due for ≥5th dose)	1.4	1.5	1.5

[a]Based on denosumab history since February 2012 (first availability) [b]Bisphosphonate history in past 365 d.

switching to another osteoporosis therapy (bisphosphonate, raloxifene, or teriparatide; romosozumab was not available through the ODB during the study period) into the definition of on-time therapy. In post hoc analyses, we updated data to plot on-time therapy until February 2022. Analyses were performed in the Institute for Clinical Evaluative Sciences (ICES) analytical environment at the University of Toronto using SAS Enterprise Guide software, version 7.1 (SAS Institute Inc.).[27]

Results

Study population

Of 170 950 patients receiving denosumab between July 2015 and July 2020, 17 395 (10.2%) were ineligible due to age < 66 yr or database errors, and another 5001 (2.9%) were excluded for evidence of malignancy (Supplementary Figure S1; Online Resource). Of the 148 554 eligible patients, 85% resided in the community at first reference dose and 91% were female (Table 1). Patients in nursing homes were older on average at first reference dose (mean age = 86.3, SD = 7.2 yr) than patients residing in the community (mean age = 78.3, SD = 7.5 yr). Approximately 73% of patients were first-time denosumab users at their first reference dose, and 40% of patients had oral bisphosphonate exposure within the year prior to first reference dose.

Trends in on-time denosumab dosing and impact of the COVID-19 pandemic

Community residents

Patients in the community contributed 565 660 denosumab doses (mean doses per patient = 4.61, SD = 3.06). The proportion of on-time denosumab doses was steady at an average of 74.4% (SD = 2.2) pre-pandemic, fluctuating between 70.0% and 78.4%. Seasonal effects were noted with drops in December of each year. In the time-series analysis, we identified an immediate 17.8% decline in the proportion of on-time denosumab doses at the start of the COVID-19 pandemic (95% CI, −19.6, −16.0) (Figure 2A). Following a low of 48.8% on-time denosumab doses in April 2020, on-time therapy recovered quickly and returned to projected levels by October 2020.

In our secondary analysis stratified by denosumab history, we identified higher pre-pandemic levels of on-time denosumab therapy among patients with a longer history of denosumab use: 64.9% (SD = 2.7; range 59.5%–69.8%) among novice users, 72.3% (SD = 2.2; range 68.8%–77.5%) among intermediate users, and 78.0% (SD = 2.2; range 72.4%–81.6%) among established users, Figure 2B. However, in contrast to our hypothesis that the impact of the pandemic would be smaller among more established users, we identified a similar absolute drop in on-time therapy regardless of user group (novice user: −15.7%, intermediate user: −18.2%, established user: −17.8%), Table 2.

Our sensitivity analysis that included switching to other osteoporosis medications to define on-time therapy made little difference in our results, with similar pre-pandemic trends and an overall immediate drop of −16.9 (95% CI, −18.7, −15.0) across all user types (Table 2). Compared to the primary +/−30 d on-time definition, our sensitivity analysis that expanded the on-time definition to +/−60 d identified an overall 8.1% increase in on-time therapy pre-pandemic (average 82.5%, SD = 1.9) and a smaller immediate reduction in

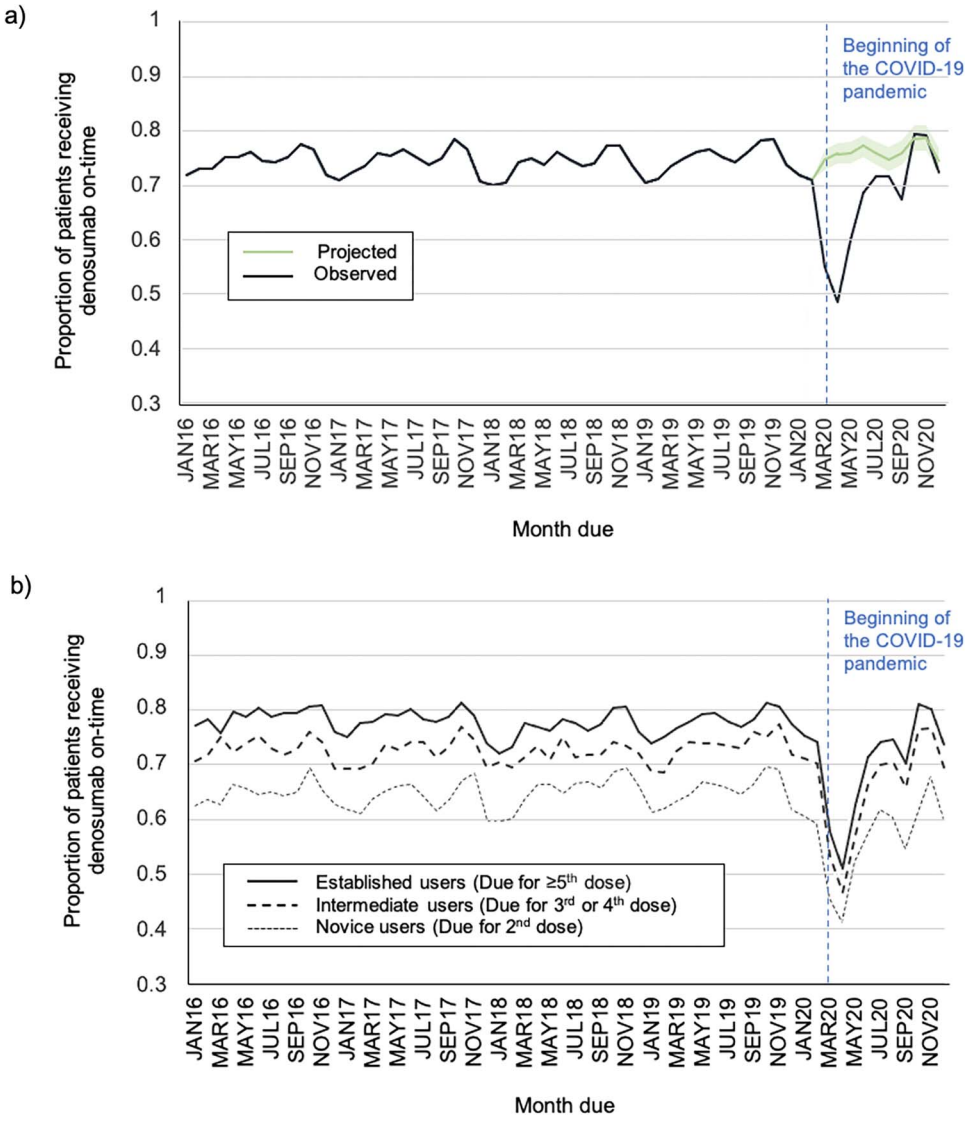


Figure 2. Proportion of patients receiving denosumab therapy on-time in the community by month due, (A) overall and (B) stratified by denosumab history.

Table 2. Intervention parameters and specified ARIMA models for community doses, $N = 565\,660$.

Outcome definition	% on-time in Feb 2020	% Reduction at pulse intervention (ω)		% Monthly recovery (δ)		ARIMA Model[a]
		ω	95% CI	δ	95% CI	$(p,d,q)\times(P,D,Q)_m$
+/−30 d						
Denosumab only						
All users	70.9	−17.75	−19.55, −15.95	54.00	47.36, 60.64	$(0,1,1)\times(1,1,0)_{12}$
Novice users (Due for second dose)	59.5	−15.67	−18.73, −12.61	46.43	31.87, 60.99	$(0,1,1)\times(1,1,0)_{12}$
Intermediate users (Due for third or fourth dose)	70.5	−18.17	−20.87, −15.47	55.77	47.31, 64.24	$(0,1,1)\times(1,1,0)_{6}$
Established users (Due for ≥5th dose)	73.7	−17.81	−19.93, −15.06	54.13	46.02, 62.24	$(0,1,1)\times(0,1,0)_{12}$
Considering medication switch						
All users	71.6	−16.85	−18.72, −14.98	57.08	50.50, 63.66	$(0,1,1)\times(0,1,0)_{12}$
+/−60 d						
Denosumab only						
All users	76.1	−13.77	−15.59, −11.95	57.61	50.22, 65.00	$(0,1,1)\times(0,1,0)_{12}$

[a]Abbreviations: ARIMA, autoregressive integrated moving average; p (P), number of (seasonal) autoregressive terms; d (D), degree of (seasonal) differencing; q (Q), number of (seasonal) moving average terms; m, degree of seasonal differencing.

on-time dosing during the pandemic: −13.8% (95% CI, −15.6, −12.0), with a low of 63.5% on-time doses in April 2020 (see Supplementary Figure S2A; Online Resource). Compared to before the pandemic, a greater proportion of patients who were due for denosumab in the early months of the pandemic did not return to therapy (discontinued denosumab) within 1 yr of their prior dose (16.2% in March 2020 and 16.8% in April 2020, compared to approximately

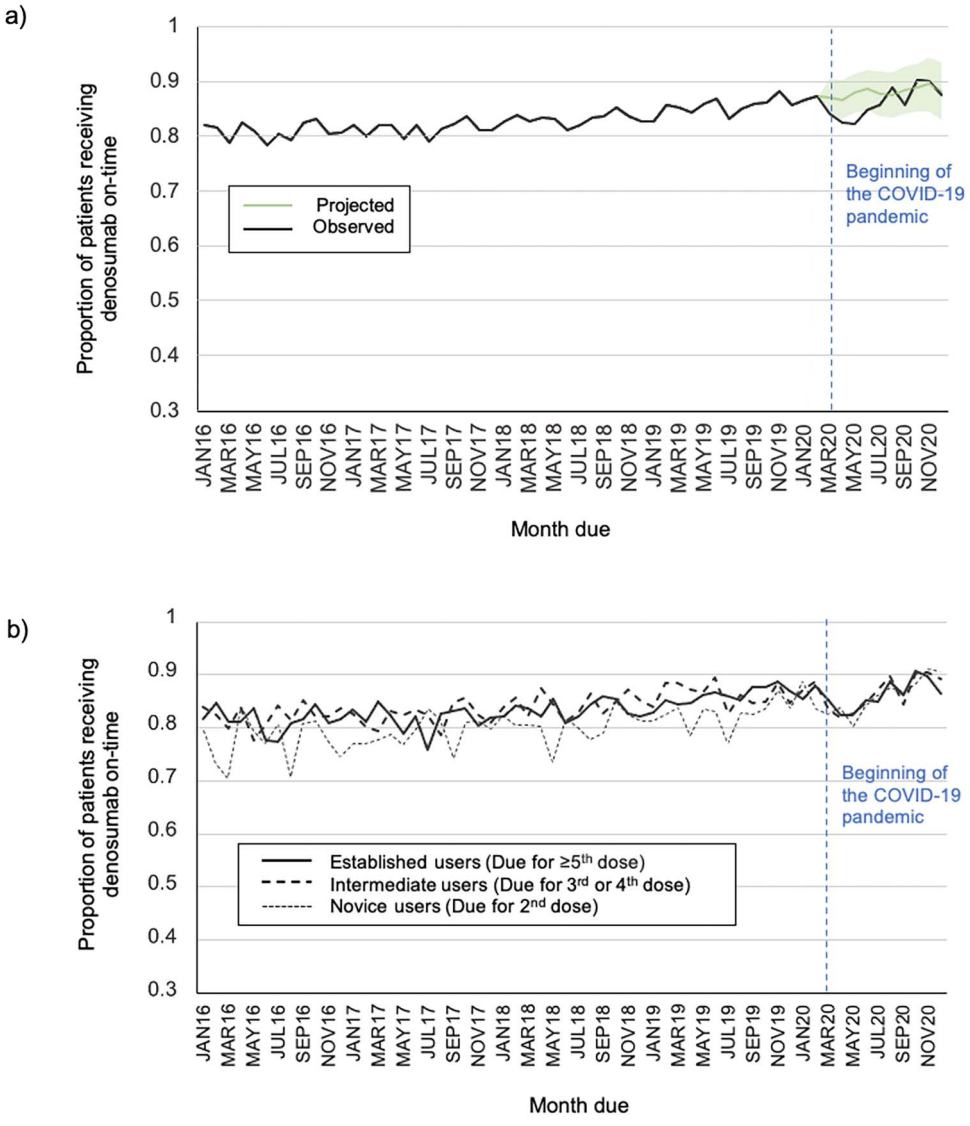


Figure 3. Proportion of patients receiving denosumab therapy on-time in nursing homes by month due, (A) overall and (B) stratified by denosumab history.

8%–10% in the months prior, Supplementary Figure S3; Online Resource). The proportion of patients not returning to therapy within 1 yr returned to pre-pandemic levels by Fall 2020.

Nursing homes

Patients in nursing homes contributed 82 561 doses (mean doses per patient = 3.53, SD = 2.51). The proportion of on-time denosumab doses increased gradually from a mean of 80.8% in 2016 (SD = 1.5, range 78.4%–83.1%) to a mean of 85.5% in 2019 (SD = 1.5, range 82.9%–88.3%). We identified a small decline in the proportion of on-time doses at the start of the COVID-19 pandemic (−3.2% [95% CI, −5.0, −1.4]) with overlap across user groups (Figure 3). On-time therapy returned to expected levels by June 2020. We observed little difference in findings when we considered switching to another osteoporosis medication (−3.2% [95% CI, −5.0, 1.3]) or when the definition of on-time therapy was expanded to +/−60 d (−2.7% [95% CI, −3.7, −1.8]), Supplementary Figure S2B in Online Resource. Furthermore, the proportion of patients who did not return to denosumab within 1 yr of their prior dose (discontinued therapy) was similar during the pandemic compared to the months before (approximately 5%–7%, Supplementary Figure S3; Online Resource).

Post hoc trends

In our post hoc descriptive analysis of on-time dosing in the community over a longer study period, we observed pre-pandemic trends in on-time therapy between January 2021 and February 2022 (mean [SD] = 73.3% [2.9], range 68.7% to 78.0%), with no major disruptions during subsequent pandemic waves. In addition, the slowly increasing pre-pandemic trend in on-time denosumab therapy in nursing homes continued after recovering from the pandemic-related drop, with a steady estimate of approximately 90% throughout 2021 (Supplementary Figure S4; Online Resource).

Discussion

Denosumab is an effective osteoporosis therapy that must be administered every 6 mo to avoid excess risk of multiple vertebral fractures. We observed an immediate sharp 18% decline

in the proportion of on-time denosumab doses in the community at the start of the COVID-19 pandemic. Given the consistency of the drop across patient groups stratified by history of denosumab use, we speculate that most of the drop was due to restricted healthcare access following mandated lockdowns and reductions in primary care visits. Indeed, it was estimated that in-person and virtual care visits combined dropped by 24% among patients aged 65–74 yr and 19% among those aged ≥75 yr in Ontario at the start of the COVID-19 pandemic.[12] Fortunately, on-time denosumab doses recovered rapidly to projected levels by the Fall of 2020, with minimal impact in subsequent waves of the pandemic. Our findings build upon previous research that identified disruptions in denosumab dosing during the pandemic.[28,29] Importantly, by conducting an interrupted time-series analysis, we were able to account for existing trends in use and revealed the temporary nature of the pandemic impact across user groups.

Our observed delays in denosumab therapy during the COVID-19 pandemic raise concerns about vertebral fracture risk. Multiple vertebral fractures have been reported as early as 2 mo after a missed denosumab injection,[3,4,30] yet we observed that less than half of community-dwelling patients who were due to receive denosumab in April 2020 received their dose within 1 mo of the due date, and only about 65% received it within 2 mo of the due date. Evidence also suggests that longer denosumab exposure is associated with greater rate of bone loss after denosumab discontinuation.[5] Thus, our finding of an 18% drop in on-time doses is particularly concerning for patients with a longer history of denosumab use. Despite guidance that patients transition to an alternate osteoporosis medication upon denosumab discontinuation or delay,[10] few patients in our study switched to an alternate therapy. Low rates of switching may partially be explained by denosumab eligibility criteria in Ontario, which include contraindication to oral bisphosphonates.[19]

Although investigating pandemic fracture rates was beyond the scope of this paper, some international evidence suggests that denosumab delays may have resulted in increased incidence of vertebral fracture. For example, a case series from an Italian hospital identified 12 cases of vertebral fracture following denosumab discontinuation in 2020–2021 compared to a total of only 8 cases in the 7 yr prior,[15] and an outpatient survey estimated that a 10% reduction in denosumab adherence during the pandemic was associated with a higher incidence of vertebral fractures.[16] Given the observed delays in on-time dosing of denosumab in Ontario during the pandemic, future work could explore whether patient outcomes were also impacted as has been observed elsewhere. This research will require careful consideration and should encompass a broader scope than diagnoses related solely to the COVID-19 pandemic. Indeed, we note inherent limitations in leveraging healthcare administrative data to estimate vertebral fracture incidence. It is estimated that only one-third of vertebral fractures come to clinical attention,[31] nearly half of vertebral fractures in North America are misdiagnosed in radiographic reports,[32] and even the most specific claims-based algorithms often result in misclassification of incident vertebral fracture.[33,34] We are most concerned about potential time trends in detection bias for identifying vertebral fractures. This concern arises not only due to a potential increase in use of X-rays to diagnose vertebral fractures over time as evidence about harms of denosumab delays became available, yet also since in-person restrictions during COVID-19 would have reduced in-person care and thus X-rays to detect vertebral fracture. We encourage future research to estimate fracture risk following denosumab discontinuation, stratified by dosing history and mindful of potential detection bias, including increased monitoring over time and the potential decline in detection during the initial period of the COVID-19 pandemic.

Despite observed denosumab delays, some of our findings are promising. The proportion of patients who receive denosumab therapy on time has increased to over 90% in nursing homes since 2016, and was minimally impacted during the pandemic. We speculate that the high rate of on-time dosing in nursing homes relates to accessible clinical support, as well as patients' ability to receive therapy without leaving their place of residence. Even in the community, the pandemic-related decline in on-time denosumab dosing was temporary. Interestingly, our observed decrease of 18% is comparable to the estimated 20% drop in *all* primary care assessments in Ontario (both in-person and virtual visits), as opposed to the 80% drop in in-person visits.[12] We speculate that virtual care facilitated timeliness of denosumab therapy. In fact, a survey of osteoporosis patients in Ontario found that patients reported high levels of comfort and quality of care associated with telemedicine during the pandemic.[35] Self-injection and home care visits may also have contributed to the timeliness of denosumab therapy during the pandemic, yet uptake of these alternatives in Ontario is unclear. Additionally, although pharmacists in Ontario did not have authority to administer drugs by injection during our study period, pharmacists did have the authority to administer denosumab for educational purposes to demonstrate self-injection,[36] and thus may have facilitated on-time therapy.

Timing of denosumab injections should remain a clinical priority as health systems continue to recover from the COVID-19 pandemic. Despite the observed return to pre-pandemic levels of denosumab timeliness in the community, the proportion of patients who receive on-time denosumab doses remains suboptimal at approximately 75%; and has not improved over time. Although some gaps in on-time therapy may result from medical circumstances (eg, delay due to an active COVID-19 infection), the overall consequences for vertebral fracture risk cannot be ignored. Considering that levels of on-time denosumab therapy remain suboptimal, future research that helps identify barriers to timely denosumab injections and strategies for improving on-time denosumab dosing is warranted.

Strengths and limitations

Our study has many strengths, including leveraging population-based data and using interrupted time-series analysis. Yet, we also acknowledge some limitations. First, dispensation data may not reflect the actual date of injection. Our estimates of on-time therapy may thus be slightly overestimated. However, since denosumab is dispensed in community pharmacies and taken by patients to clinical appointment for injection, we anticipate minimal measurement error related to date of denosumab injections estimated by pharmacy dispensation date. Second, we recognize potential selection bias among patients due for denosumab in late September 2020, since patients due for denosumab must have received a denosumab dose 6 mo earlier, during the height of the first wave of the pandemic. Patients who received denosumab early during COVID-19 lockdowns may have been inherently more adherent to therapy, making them more likely to receive an

on-time dose at their next due date. For example, patients with more comorbidities or concurrent medication use may have been less adherent (less likely to be willing to go to an in-person appointment to receive denosumab) during the start of the pandemic. Selection for more adherent patients could have facilitated the observed rapid recovery rate. Similarly, survivor bias, particularly in nursing homes, may have falsely elevated our estimates of on-time denosumab dosing in the Fall of 2020 and underestimated the potential impact of the pandemic. However, given that our post hoc analysis through to February 2022 identified similar trends in on-time denosumab dosing as before the pandemic, we are confident in our conclusions that the impact of the pandemic on the proportion of patients receiving denosumab doses on time was immediate yet temporary. Third, it is possible that history of denosumab exposure was underestimated among younger patients, since ODB data only cover residents aged 65 or more years and we included patients aged 66 or more years. However, with mean age of 79.6 (SD = 8.0) yr at initiation, we believe errors in categorization of novice (due for second dose), intermediate (due for third or fourth dose), and established (due for ≥5th dose) would have minimal impact on findings.

Despite some limitations, our population-based longitudinal claims database permitted us to comprehensively evaluate denosumab use for all older Ontario residents. To our knowledge, we are not only the first to use interrupted time-series analysis to adjust for baseline trends, yet also the first to consider patient history of denosumab exposure. We were thus able to quantify the immediate impact and recovery in denosumab timeliness after the start of the COVID-19 pandemic in the community and nursing homes, and by patient denosumab histories.

Conclusions

In this population-based study, we identified an immediate yet temporary decrease in on-time denosumab therapy at the start of the COVID-19 pandemic. Although the proportion of on-time doses returned to pre-pandemic levels by the Fall of 2020, the proportion of patients in the community who receive denosumab on time remains sub-optimal at approximately 75%. Future research should assess the impact of pandemic denosumab delays on vertebral fracture rates, and consider barriers and solutions to promote on-time denosumab therapy.

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Author contributions

Anna M. Rzepka (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing—original draft, Writing—review & editing), Angela M. Cheung (Conceptualization, Methodology, Writing—review & editing, Sandra Kim (Conceptualization, Writing—review & editing), Tara Gomes (Conceptualization, Methodology, Writing—review & editing), and Suzanne M. Cadarette (Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing—review & editing)

Supplementary material

Supplementary material is available at *JBMR Plus* online.

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Conflicts of interest

A.M.R., S.K., T.G., and S.M.C. declare that they have no conflicts of interest. A.M.C. served as a consultant for Amgen Inc. outside of this work.

Data availability

The dataset from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers (eg, healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Ethical approval

ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorized under section 45 and approved by ICES' Privacy and Legal Office.

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