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ORIGINAL REPORT

Adherence to osteoporosis pharmacotherapy is underestimated using days supply values in electronic pharmacy claims data†

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ABSTRACT

Purpose Days supply (prescription duration) values are commonly used to estimate drug exposure and quantify adherence to therapy, yet accuracy is not routinely assessed, and potential inaccurate reporting has been previously identified. We examined the impact of cleaning days supply values on the measurement of adherence to oral bisphosphonates.

Methods We identified new users of oral bisphosphonates among Ontario seniors (April 2001–March 2011). Days supply values were examined by dose, and we identified misclassification by comparing observed values to dose-specific expected values. Days supply values not matching expected values were cleaned using dose-specific algorithms. One-year adherence to therapy was defined using measures of compliance (mean proportion of days covered [PDC], and categorized into high [PDC $\geq$ 80%], medium [50% $<$ PDC $<$ 80%], low [PDC $\leq$ 50%]) and persistence (30-day permissible gap). Estimates were compared using the observed and cleaned days supply values, stratified by site of patient residence (community or long-term care [LTC]).

Results We identified 337 729 (5% LTC) eligible new users. Among LTC patients, adherence estimates increased significantly following data cleaning: mean PDC (59 to 83%), proportion with high compliance (47 to 76%), and proportion persisting with therapy (62 to 78%). Modest increases were identified among community-dwelling patients following data cleaning (mean PDC, 71 to 74%; high compliance, 54 to 58%; and persistence, 56 to 61%).

Conclusions Data cleaning to correct for exposure misclassification can influence estimates of adherence with oral bisphosphonate therapy, particularly in LTC. Results highlight the importance of developing data cleaning strategies to correct for exposure misclassification and improve transparency in pharmacoepidemiologic studies. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—exposure misclassification; days supply; adherence; pharmacy claims data; pharmacoepidemiology

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INTRODUCTION

Suboptimal adherence to medications for chronic asymptomatic diseases among seniors is a major public health concern.[1,2] Nevertheless, inconsistent adherence estimates have hindered cross-study comparisons, particularly in the area of osteoporosis.[3] Researchers frequently utilize large pharmacy claims data to examine drug exposure, safety, and effectiveness.[4] While studies have identified the completeness of pharmacy claims data,[5–7] few have examined the accuracy of days supply values for measuring drug exposure.[6,8] As the only measure of prescription duration in pharmacy claims data, the days supply field is one of the most commonly used to estimate drug exposure and quantify adherence to therapy.[5,6,8,9] Indeed, days supply is used in the calculation of medication compliance and persistence.[9] The accuracy of days supply values is therefore crucial for obtaining valid estimates of drug adherence

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and drug effects,[8] yet the accuracy of days supply values are not routinely assessed by claim adjudicators.

We previously identified variation in days supply reporting for osteoporosis medications with fixed dosing intervals.[10] This variation was particularly evident among prescriptions dispensed to long-term care (LTC) residents, where an underestimation of days supply was common. Thus, while pharmacy claims data bypass the potential for recall bias inherent in self-report, exposure misclassification can occur when relying on pharmacy claims data and lead to biased estimates of drug exposure.[11] However, the impact of inaccurate (misclassified) days supply reporting on the measurement of medication adherence is unknown, and few studies have examined data cleaning strategies.[6,8,12] In this study, we examined the impact of misclassified days supply values on estimates of adherence to osteoporosis medications.

METHODS

Cohort identification

We used health care administrative claims data (medical and pharmacy) to identify new users of oral bisphosphonates among Ontario seniors. In Ontario, all residents receive universal access to medical and hospital services, and complete drug coverage is provided through the Ontario Drug Benefit (ODB) program for residents aged 65 years or older (seniors). The ODB database contains information on all covered medications to patients residing in the community or in nursing homes (LTC). The database includes detailed information for each dispensing record, including a unique patient identifier, date that the prescription was dispensed, drug identification number, drug name, dose, quantity (number of units/pills), days supply (prescription duration), and a flag indicating patient residence (community or LTC). The quantity and drug identification number are used to determine pharmacy reimbursement, while the days supply is entered by the pharmacist to estimate prescription duration (number of days that a patient will be covered by the medication dispensed) and identifies early or late refills.

New users of oral bisphosphonates were identified among Ontario seniors aged 66 years or older from 1 April 2001 to 31 March 2011, with follow-up through to 31 March 2012. Eligible oral bisphosphonates included osteoporosis formulations of alendronate (10 and 70 mg), etidronate (400 mg etidronate and 500 mg calcium), and risedronate (5, 35, and 150 mg). The first date of dispensing for an eligible bisphosphonate was considered the index date. Patients with bisphosphonate use in the year prior to the index date were excluded. Switching to other osteoporosis medications (calcitonin, denosumab, raloxifene, or zoledronic acid) during follow-up was permitted.

We excluded patients receiving non-osteoporosis formulations of bisphosphonates (e.g., clondronate or pamidronate) and men receiving estrogen therapy. To increase the probability that patients received bisphosphonate therapy for osteoporosis, we further excluded patients that had a diagnosis for a condition that may impact bone quality and have a different oral bisphosphonate dosing: celiac disease, Cushing's syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasm, osteomalacia, osteopetrosis, Paget's disease, organ transplant, and renal impairment or dialysis.

Data cleaning

Reporting on the optimal method to clean days supply is scarce, particularly in the area of osteoporosis. We cleaned data by adjusting for duplicate records and misclassified days supply. First, we examined duplicate records to distinguish between travel supplies and claim retractions. It is common practice to remove duplicate records as they are often considered to be errors in data entry (e.g., claim retractions not captured in the database). However, duplicate entries may be indicators of extended travel. In Ontario, to permit travel extending beyond 100 days (the maximum days supply permitted in the ODB), seniors can receive a travel supply of their medication. Travel supplies can total a maximum of 200 days (e.g., two 100-day prescriptions) and would be dispensed on the same day.[13] In our analysis, prescription records were identified as eligible travel supplies if as follows: (i) sum of days supplied was >100 days; (ii) duplicate records were for the same drug and dosing regimen; and (iii) time to the next prescription fill was $>75\%$ of the sum of the days supplied, or there was no subsequent refill. All prescription records identified as travel supplies were included as eligible prescriptions. Remaining duplicate records were deemed to be ineligible (e.g., errors or retractions), with only one prescription claim included per person and day. All subsequent data cleaning was completed following the removal of ineligible duplicate records.

Second, days supply values that did not match the predefined dose-specific expected days supply (Table 1) were identified and examined to identify dispensing patterns and guide data cleaning. The first pattern identified was *logical typos* made during data entry. Based on prior literature,[14] we examined the possibility that quantity was entered into the days supply. In these

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Table 1. Definition of dose-specific expected days supply values and sample data cleaning and rationale

		Worked example of unexpected days supply and data cleaning strategy*					
Regimen	Predefined expected days supply values†	Observed quantity	Observed days supply	Expected days supply	Observed days to refill	Imputed cleaned days supply	Pattern definition‡
Daily§	Quantity dispensed	30	25	30	n/a	30	Quantity dispensed automatically imputed
Weekly	7 or 30-day intervals	4	4	28 or 30	n/a	30	Logical typo: quantity imputed as days supply
Monthly	28 or 30-day intervals	1	7	28 or 30	30	30	Packaging: likely weekly dispensing in LTC
Cyclical¶	90 days	1	100	90	n/a	90	Logical: likely imputed ODB maximum
Annual	365 days	1	100	n/a‖	n/a	365	No expected—365 automatically imputed
Semiannual	180 days	1	3	n/a‖	n/a	180	No expected—180 automatically imputed

*Example of data cleaning used in the Ontario Drug Benefit (ODB) Database for osteoporosis medications. It identified the relationship between the observed quantity dispensed and the observed days supply in relationship to the expected values to determine data cleaning strategies. The number of days to the next refill was used to guide data cleaning for entries not explainable through logical typos.

†Adapted from Burden *et al.* (2013). Arch Osteoporos.[10]

‡Patterns were identified as logical typos (e.g., easily explainable patterns in data entry), compliance packaging (e.g., refill patterns indicate that patients' medication was dispensed weekly—regardless of regimen), or random typos (e.g., potential data entry typos identified using the quantity, days supply, and number of days to the next refill).

§Expected days supply for daily medications not identified. Instead, the quantity dispensed was imputed as the most accurate measure of days supply. All daily medications are dispensed as one pill per day, and quantity is used to determine reimbursement. Thus, quantity is likely a more accurate measure of duration.

¶Ontario Drug Benefit billing is per package containing 14-day-active drug plus 76 days calcium. Therefore, THE expected days supply is 90 days with quantity of one.

‖Expected days supply values for annual IV (zoledronic acid) and semiannual IV (denosumab) not identified as the expected value is beyond the 100-day maximum allowed in the ODB. Patients are permitted to switch to annual or semiannual formulations during follow-up.

cases, the cleaned days supply value would be the quantity multiplied by the therapeutic dose interval. Next, we examined the potential that some days supply values for medications with monthly or cyclical intervals were reduced to accommodate *compliance packaging*. To improve adherence, prescribers may request that medications be dispensed in weekly blister packs to improve medication adherence, resulting in unexpected days supply values. Finally, if values were not identified as logical typos or indicators of compliance packaging, they were classified as *random typos*. Here, the relationship between the observed days supply, the observed quantity, and the days between refills was used to determine the appropriate cleaned days supply. This process generated dose-specific data cleaning algorithms and resulted in two days supply values, the observed (original days supply) and the cleaned (created using the previously mentioned cleaning algorithm). Examples of data cleaning strategies are provided in Table 1.

Adherence measurement

We identified 1-year adherence using measures of compliance and persistence.[9,15] Compliance to therapy was defined as the proportion of days covered (PDC), and persistence was defined using a 30-day permissible gap.[9] While a 30-day permissible gap is consistent with prior research on persistence with osteoporosis pharmacotherapy,[3,16] secondary analyses used a 60-day permissible gap and 50% grace period (1.5 times the days supply) to identify non-persistence. Medications dispensed in hospital are not captured in the ODB database; thus, analyses were adjusted for hospitalization days.[9,17] Early refills of the same drug and dose were considered additive (cumulative use), while switches between drugs or dosing regimens were considered a complete switch with no overlap granted. Patient observation time ended at the first of death, entry into LTC for community-dwelling patients, or the end of the 1-year observation period. Compliance and persistence were calculated separately for the observed and cleaned days supply values and stratified by residential status (community or LTC) at the index date. Figure 1 illustrates an example of the potential impact of data cleaning on estimates of compliance and persistence.

Data analysis

Patient descriptive characteristics (i.e., age, sex, osteoporosis diagnosis, prior bone density test, prior fracture, and prior hospitalization) were summarized at the index date. Compliance at 1 year was summarized continuously as mean and median PDC and

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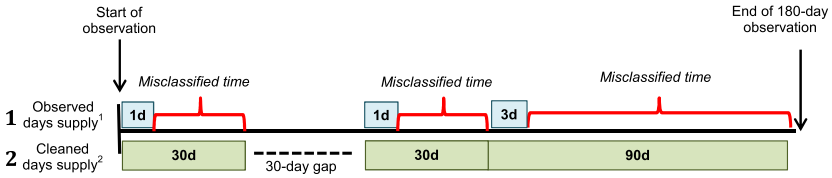

	No. of days supplied	No. days denominator	PDC[3], %	Days persisted with therapy: ≥30-day permissible gap	≥60-day permissible gap	50% grace period
1. Observed	1+1+3 = 5	180	2.8	1	93	1.5
2. Cleaned	30+30+90 =150	180	83.3	30	180	180

Figure 1. Impact of data cleaning on measurement of compliance and persistence for hypothetical example patient receiving monthly risedronate for a 6-month (180-day) period. (1) Observed days supply represents the value (number of days) entered electronically at the time of dispensing. (2) Cleaned days supply represents the value (number of days) imputed during data cleaning. (3) Proportion of days covered (PDC) calculated as the number of days supplied divided by the total number of days in the observation period

categorically as high (PDC ≥ 80%), medium (50% < PDC < 80%), or low (PDC ≤ 50%) compliance. Persistence was summarized as the proportion persistent at 1 year. The absolute differences between estimates of compliance and persistence obtained using observed and cleaned days supply values were calculated. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina). The protocol for this study was approved by the Research Ethics Boards at Sunnybrook Health Sciences Centre in Toronto and the University of Toronto.

RESULTS

We identified 337 729 new users of bisphosphonates meeting our inclusion criteria (5%, residing in LTC), with 10 346 678 pharmacy claims (25% LTC), Figure 2. Patients in LTC were older (mean age: 84 vs 75 years) at index prescription. In the year prior to index therapy, LTC patients were less likely to have a diagnosis of osteoporosis (14 vs 39%) or had a bone density test (10 vs 67%), yet more patients had a fracture (33 vs 8%) or were hospitalized (52 vs 15%), Table 2.

We identified 120 864 (1%) potential duplicate prescription claims in 22 538 (6%) patients. Approximately two thirds ($n = 76\,863$ [64%]) met our criteria for travel supplies, for which we included both records. For the remaining ($n = 44\,001$ [36%]), we included one record per patient. Ineligible duplicate records were removed from both the observed and cleaned days supply cohorts. Among days supply values, 10% of daily (9% in community and 18% in LTC), 14% of weekly (8% in community and 39% in LTC), 21% of monthly (9% in community and 65% in LTC), and 17% or cyclical etidronate (15% in community and 51% in LTC) regimens did not match the expected days supply and required data cleaning. With a 100-day maximum days supply permitted, all values for semiannual and annual regimens were cleaned. The most common reasons for misclassification were logical typos (37%; 27% in community and 47% in LTC) and random typos (49%; 49% in community and 47% in LTC).

Estimates of compliance and persistence were greater using the cleaned versus the observed days supply, with larger differences noted among LTC residents, Table 3. Among LTC residents, mean PDC increased from 59% (standard deviation [SD] = 41%) to 83% (SD = 32%) and median PDC from 73% (interquartile range [IQR] = 86) to 100% (IQR = 16). When categorized into PDC groups, there was a shift from low to high compliance, with high compliance increasing from 47 to 76% and low compliance decreasing from 45 to 17%. Among community residents, data cleaning resulted in relatively modest increases in mean PDC (70% [SD = 34%] to 74% [SD = 32%]), median PDC (87% [IQR = 60%] to 96% [IQR = 51%]), and the proportion identified with high compliance (54 to 58%).

In LTC, the proportion of patients that persisted with therapy increased by 16% (68 to 80%) using a 30-day gap, 12% (62 to 78%) using a 60-day gap, and 32% (40 to 72%) using a 50% grace period. Modest increases of 40 to 6% were observed among community residents, Table 3.

DISCUSSION

While pharmacy claims are a rich, cost-efficient data source for drug safety and effectiveness research, there are important methodological challenges, including the potential for exposure misclassification when using the observed days supply values. In our setting of fixed-dose osteoporosis therapy for older adults, we identified that not accounting for potential misclassification of days supply values led to important

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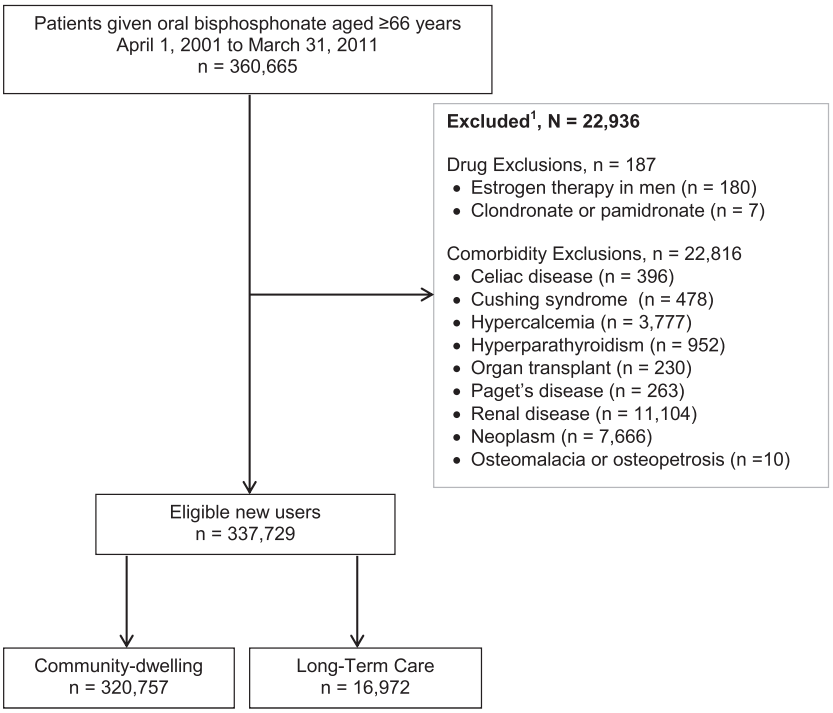

Figure 2. Flow diagram of cohort identification, April 2001–March 2011. (1) Exclusions not mutually exclusive. All exclusions identified in the year prior to index therapy. Drug exclusions identified using the Ontario Drug Benefit (ODB) database and all comorbidity exclusions identified using ICD-9-CM and ICD-10-CA codes from the Ontario Health Insurance Plan database, Discharge Abstract Database (Canadian Institute for Health Information Discharge Abstract Database), and the National Ambulatory Care Reporting System database

underestimation of both compliance and persistence, particularly in the LTC setting.

There remains limited evidence on the impact of days supply misclassification on measurement of medication adherence. Two previous studies identified minimal difference when using a researcher-derived days supply for daily antiretroviral medications[8] or long-acting antipsychotics.[18] While our results identified a greater impact of data cleaning in the LTC setting, our community results are comparable to previous studies. Gross *et al*. identified an 8% misclassification among daily antiretroviral medications, when compared with researcher-derived days supply values, and estimated minimal impact of misclassification when estimating compliance.[8] Similarly, we identified a 9% potential misclassification among daily dispensed medications and would anticipate little change in estimates of compliance or persistence among these medications in the community setting.

Table 2. Characteristics of new users of oral bisphosphonates aged 66 or more years, April 2001–March 2011, stratified by site of residence

	Community $n = 320\,757$		LTC $n = 16\,972$		All patients $n = 337\,729$	
	n	%	*n*	%	*n*	%
Age, mean (SD)	75.2	6.8	84.4	7.1	75.7	7.1
Female	257 767	80.4	13 558	79.9	271 325	80.3
Osteoporosis diagnosis	123 312	38.5	2417	14.2	125 729	37.2
BMD test*	216 186	67.4	1753	10.3	217 939	64.5
Prior fracture†	26 525	8.3	5635	33.2	32 160	9.5
Prior hospitalization	47 389	14.8	8872	52.3	56 261	16.7

SD, standard deviation.

*Osteoporosis diagnosis and bone mineral density (BMD) testing identified within 1 year prior to the index date using Ontario Health Insurance Plan billing codes.

†Fractures were identified using International Classification of Diseases (ICD)-9 Clinical Modification and ICD-10 Canada codes in the year prior to index therapy.

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Table 3. Percentage of patients who were compliant and persistent with oral bisphosphonate therapy using the observed and cleaned days supply, stratified by site of residence

	Community $n = 320\,757$			Long-term care $n = 16\,972$			All patients $n = 337\,729$		
Days supply	Observed	Cleaned	Change	Observed	Cleaned	Change	Observed	Cleaned	Change
Compliance*									
Mean (SD)	71 (34)	74 (32)	+3	59 (41)	83 (32)	+24	70 (34.2)	75 (32)	+5
Median (IQR)	87 (60)	96 (51)	+9	73 (86)	100 (16)	+27	87 (65)	99 (51)	+12
Compliance groups†									
High, %	54	58	+4	47	76	+29	54	59	+5
Medium, %	15	15	—	8	7	−1	15	15	—
Low, %	31	27	−4	45	17	−28	31	26	−5
Persistence									
30 days, %	56	61	+5	62	78	+16	56	62	+6
60 days, %	66	70	+4	68	80	+12	66	71	+5
50% grace period, %	56	62	+6	40	72	+32	55	62	+7

SD, standard deviation; IQR, interquartile range.
*Compliance defined using the proportion of days covered (PDC) and calculated as the number of days supplied in 1 year, divided by 365 days, minus the number of days in hospital. All PDC values are capped at 1 or 100%.
†Compliance groups defined using PDC: high (PDC ≥ 80%), medium (50% < PDC < 80%), and low (PDC ≤ 50%).

Days supply misclassification may be unique to longer dose medications and potentially emphasized in LTC settings. Indeed, a recent study by Campagna *et al*. examined strategies to clean days supply values for monthly injectable antipsychotics among community-dwelling patients. Authors identified a 4–6% change in PDC and a 3–5% change in persistence (using an 11 to 30-day gap).[18] Thus, our results, similar to others, emphasize that the dosing regimen, population, and choice of cleaning strategy can greatly impact measurement of adherence.

In our study, we identified that correcting days supply values, using dose-specific and database-specific cleaning algorithms, improved adherence estimates. In particular, estimates of variation in mean and median PDC (SD and IQR) were reduced following data cleaning, suggesting greater reliability. Adjusting the permissible gap length used to define persistence with therapy highlighted the impact of misclassified days supply values. The greatest misclassification was observed when a 50% grace period was used to define non-persistence in LTC, where exposure is most likely to be underestimated.[10] While longer gap lengths reduced the impact of misclassification, specificity may be compromised. Careful consideration of data accuracy and the definition of compliance (mean, median, and categories) and persistence (gap length) is therefore required.

These findings speak to the possible methodological implications when quantifying adherence using administrative claims data. Many factors may influence non-adherence, yet our results identify that data cleaning can influence estimates of adherence. Thus, greater transparency in reporting, and more consistent data cleaning strategies, may improve the accuracy of estimates and permit cross-study comparisons.[2,3] This recommendation is consistent with a previously published checklist for studies of adherence using administrative data.[15] However, while the checklist requires that evidence of data accuracy and/or data cleaning be clearly presented, we were unable to identify studies that have performed this when using the days supply to measure adherence. Thus, greater scrutiny in methodological reporting, particularly around the operationalization of adherence, and in the analytic steps to identify and/or correct for exposure misclassification in the days supply is needed.

While pharmacy claims data are often considered reliable sources for identifying real-world drug utilization,[5,12] our results show that misclassification of exposure can occur. This is particularly true if drugs are prescribed on an "as needed basis," if patients do not take medications as indicated, or there is an underestimation of duration. Our results identify the potential for exposure misclassification to occur when using observed days supply values and highlight the importance of understanding potential system-level factors that may influence data entry. For example, days supply may be underestimated purposefully to avoid claim rejections for early refills or as an indication of weekly compliance packaging. Indeed, in the LTC setting, we identified a tendency toward short-cycle dispensing.[10] This practice may be common in facilities where medications are frequently dispensed in weekly compliance packaging to limit medication errors and storage.[19] Despite system-level factors that

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may explain days supply misclassification, the development of educational strategies that can be implemented at the pharmacy level may be crucial to improve reporting accuracy, particularly for medications with longer dose intervals. At minimum, we recommend the education of pharmacy students of the application of pharmacy claims data for research purposes and the importance of accurate data entry.

While general educational strategies may improve reporting, it is important to note that some system-level factors may inhibit accurate reporting of days supply for long-dose medications. For example, LTC residents in Ontario are exempt from the public drug plan policies that limit the days supply, or the number of paid dispensing in a 30-day period, yet this may not be common elsewhere. In the US Medicare Part D Program, a short-cycle policy was recently introduced and restricts LTC medications to a 14-day maximum.[20] Such policies may influence how pharmacists enter the days supply for medications with dosing intervals exceeding the 14-day maximum and should be closely examined prior to data analysis. In these instances, an unexpected days supply for a monthly medication is logical yet requires correction prior to data analysis to accurately capture a patient's drug history.

In interpreting our results, some limitations are worth noting. When cleaning days supply values, the expected value (i.e., therapeutic dosing interval) was imputed if the patient did not have a subsequent refill. This may have resulted in an overestimation of true exposure if the patient did not take the medication dispensed. Nevertheless, this occurred in $<1\%$ of cases, so we expect the impact to be minimal. In addition, we only examined data from a single Canadian province (Ontario) and therefore emphasize the importance of examining data quality and using drug and database-specific cleaning strategies. For example, the Medicare Part D short-cycle rule in LTC will likely result in an underestimation of medications with monthly or longer dosing intervals, similar to our findings.[20] Another limitation is our classification of logical, random, and packaging errors. This classification was based on researcher-derived definitions that were data driven, with no primary data collection. It is therefore possible that some random or logical typos were indicators of pill packaging. Finally, we only studied osteoporosis medications as a case example because of the fixed dosing interval of the medications, and therefore, results may not be generalizable. However, we believe that our results are generalizable to other medications with extended or fixed dosing (e.g., birth control and long-acting schizophrenia medications)[21] and note that extended dose medications may become more common for chronic disease management (e.g., new long-acting HIV medications).[22]

Despite noted limitations, our study has a number of strengths. We studied a population-based cohort of over 300 000 new users of oral bisphosphonates and over 10 million dispensing records. To our knowledge, this analysis is the first to closely examine duplicate records and identify the prevalence of travel supplies. Duplicate entries are commonly considered erroneous entries and are often excluded from analyses.[23,24] However, in Canada, it is estimated that over 400 000 seniors will leave the country during the winter months.[25] These "snowbirds" are generally healthy seniors who routinely fill prescriptions prior to travelling for periods beyond the 100-day maximum drug supply.[13,26] Thus, removing duplicate records among these seniors will result in differential exposure misclassification, whereby potentially healthy and adherent individuals appear to be non-adherent with extended (up to 90 days) gaps in use. Our analysis will therefore inform best practices, where it is common practice to only include a single prescription when duplicates are identified. A second strength was using multiple gap lengths to identify the impact of data cleaning on estimates of persistence. We found that using a 50% grace period, the most commonly used to avoid misclassification,[4] resulted in the greatest underestimation of adherence. Our study also examined dispensing practices by site of patient residence, noting significant differences in LTC. Thus, where feasible, we encourage future studies of medication adherence to examine LTC patients separately. In addition to the methodological implications of this work, our results highlight the importance of future research directed at developing educational strategies to improve days supply reporting at the pharmacy level, particularly within LTC pharmacies.

CONCLUSIONS

In our study, misclassified days supply values led to an underestimation of medication compliance and persistence, particularly among LTC residents. Few studies report whether steps were taken to clean pharmacy data, thereby making cross-study comparisons difficult. Greater transparency in methodological reporting is therefore needed. Our results highlight key methodological implications and speak to the importance of understanding the data source (e.g., patients and data entry process) when investigating and correcting for misclassification. We expect data cleaning algorithms to be database and drug-class specific and therefore emphasize the need for transparency in methodological

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reporting. The development of data cleaning and reporting strategies to correct for drug exposure misclassification is important to achieving accurate estimates of drug safety and effectiveness when using administrative claims data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- Days supply values are commonly used to quantify measures of adherence, yet little information on the potential for misclassification exists.
- Results identify that measures of adherence are underestimated without data cleaning to correct for exposure misclassification.
- Data cleaning strategies to correct for misclassification should be drug and database specific.
- Transparency in methods to examine accuracy and data cleaning strategies is encouraged.

ETHICS STATEMENT

The protocol for this study was approved by the Research Ethics Boards at Sunnybrook Health Sciences Centre in Toronto and the University of Toronto.

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REFERENCES

1. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Effectiveness of interventions by community pharmacists to improve patient adherence to chronic medication: a systematic review. *Ann Pharmacother* 2005; **39**: 319–328. doi:10.1345/aph.1E027.
2. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int* 2007; **18**: 1023–1031. doi:10.1007/s00198-006-0322-8.
3. Kothawala P, Badamgarav E, Ryu S, Miller RM, Halbert RJ. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. *Mayo Clin Proc* 2007; **82**: 1493–1501. doi:10.1016/S0025-6196(11)61093-8.
4. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005; **58**: 323–337. doi:10.1016/j.jclinepi.2004.10.012.
5. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003; **10**: 67–71.
6. Farris K, Kaplan B, Kirking DM. Examination of days supply in computerized prescription claims. *J Pharmacoepidemiol* 1994; **3**: 63–76.
7. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol* 1995; **48**: 999–1009.
8. Gross R, Bilker WB, Strom BL, Hennessy S. Validity and comparison of two measures of days supply in Medicaid claims data. *Pharmacoepidemiol Drug Saf* 2008; **17**: 1029–1032. doi:10.1002/pds.1606.
9. Cadarette SM, Burden AM. Measuring and improving adherence to osteoporosis pharmacotherapy. *Curr Opin Rheumatol* 2010; **22**: 397–403. doi:10.1097/BOR.0b013e32833ac7fe.
10. Burden AM, Huang A, Tadrous M, Cadarette SM. Variation in the days supply field for osteoporosis medications in Ontario. *Arch Osteoporos* 2013; **8**: 128. doi:10.1007/s11657-013-0128-1.
11. Strom BL. Methodologic challenges to studying patient safety and comparative effectiveness. *Med Care* 2007; **45**: S13–S15. doi:10.1097/MLR.0b013e318041f752.
12. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a prescription claims database to estimate medication adherence in older persons. *Med Care* 2006; **44**: 471–477. doi:10.1097/01.mlr.0000207817.32496.cb.
13. Ministry of Health and Long-Term Care. The Ontario Drug Benefit Program - If you Travel. Available at: http://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/opdp_travel_supply.aspx. Accessed March 24, 2014.
14. Jackevicius CA, Paterson JM, Naglie G. Concordance between discharge prescriptions and insurance claims in post-myocardial infarction patients. *Pharmacoepidemiol Drug Saf* 2007; **16**: 207–215. doi:10.1002/pds.1289.
15. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 2007; **10**: 3–12. doi:10.1111/j.1524-4733.2006.00139.x.
16. Rabenda V, Mertens R, Fabri V, *et al.* Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. *Osteoporos Int* 2008; **19**: 811–818. doi:10.1007/s00198-007-0506-x.
17. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol* 2008; **168**: 329–335. doi:10.1093/aje/kwn135.
18. Campagna EJ, Muser E, Parks J, Morrato EH. Methodological considerations in estimating adherence and persistence for a long-acting injectable medication. *J Manag Care Pharm* 2014; **20**: 756–766. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24967528. Accessed August 5, 2014.
19. Long-term-care Homes - Medication Management. Office of the Auditor General of Ontario Annual Report 2007; 232–258.
20. Barlas S. New medicare part d rule affects long-term-care pharmacies. *Pharm Ther* 2011; **36**: 319.
21. Rosenheck RA, Krystal JH, Lew R, *et al.* Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 2011; **364**: 842–851. doi:10.1056/NEJMoa1005987.
22. Spreen WR, Margolis DA, Pottage JC. Long-acting injectable antiretrovirals for HIV treatment and prevention. *Curr Opin HIV AIDS* 2013; **8**: 565–571. doi:10.1097/COH.0000000000000002.
23. Gold DT, Martin BC, Frytak JR, Amonkar MM, Cosman F. A claims database analysis of persistence with alendronate therapy and fracture risk in postmenopausal women with osteoporosis. *Curr Med Res Opin* 2007; **23**: 585–594. doi:10.1185/030079906X167615.
24. Mudd KE, Bollinger ME, Hsu VD, Manning A, Tsoukleris MG, Butz AM. Concordance of Medicaid and pharmacy record data in inner-city children with asthma. *Contemp Clin Trials* 2008; **29**: 13–20. doi:10.1016/j.cct.2007.05.002.
25. Coates KS, Healy R, Morrison WR. Tracking the Snowbirds: Seasonal Migration from Canada to the U.S.A. and Mexico. *Am Rev Can Stud* 2002; **32**: 433–450.
26. Marshall VW, Longino CF, Tucker R, Mullins L. Health care utilization of Canadian snowbirds: an example of strategic planning. *J Aging Health* 1989; **1**: 150–168.