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Examining Exposure Misclassification of Oral Bisphosphonate Therapy and the Associated Fracture Risk: A Cohort Study

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Abstract

Introduction: Using pharmacy claims data we previously identified exposure misclassification in pharmacy claims data that underestimated oral bisphosphonate compliance, particularly in long-term care (LTC). In this study we examined the impact of exposure misclassification in pharmacy claims data on estimates of drug effectiveness using osteoporosis pharmacotherapy and hip fractures as a case example.

Methods: We identified new users of oral bisphosphonates, aged 66 or more years, using Ontario claims data. Compliance was quantified by the proportion of days covered (PDC) and categorized into groups during a 365-day ascertainment period. PDC was calculated using observed and cleaned days supply values. Hip fracture rates were calculated using Cox proportional hazard models, adjusted for behavioral and fracture risk factors. Low compliance (PDC < 20%) was the referent. Analyses were completed overall and separately for patients in community and LTC settings.

Results: The rate of hip fracture was higher in LTC (2.4/100 patient-years) than in the community (1.0/100 patient-years). Following data cleaning, to adjust for exposure misclassification, the estimated benefit of high compliance (PDC ≥ 80%) on fracture prevention ($HR_{observed}$ = 0.74, 95% CI = 0.66-0.83; $HR_{cleaned}$ = 0.65, 95% CI = 0.57-0.74) increased. Risk estimates were similar among community-dwelling patients ($HR_{observed}$ = 0.68, 95% CI = 0.60–0.77; $HR_{cleaned}$ = 0.65, 95% CI = 0.56–0.75), yet differed substantially in LTC ($HR_{observed}$ = 0.96, 95% CI = 0.73–1.26; $HR_{cleaned}$ = 0.64, 95% CI = 0.46–0.91).

Conclusion: Exposure misclassification can bias estimates of drug effectiveness. While minimal change was noted in the community setting where most studies are completed, large differences were noted in LTC where fracture risk was highest. These results highlight the importance of understanding and examining the potential for exposure misclassification prior to data analysis in pharmacoepidemiology, particularly when including LTC settings.

Keywords: Compliance; Exposure misclassification; Claims data; Osteoporosis; Hip fracture

Introduction

Osteoporosis is a major public health concern resulting in significant fracture morbidity and mortality [1-3]. Hip fractures are the most serious consequence of osteoporosis and result in significant morbidity, mortality, and social costs [4-6]. Several effective treatments exist to reduce a patient's risk for fracture, yet 30% to 50% of patients will become non-compliant within the first year of treatment initiation [7-9]. Unfortunately, poor medication compliance is associated with a reduced clinical benefit and increase in hip fracture risk [10-14]. Previous studies have identified that high compliance with osteoporosis medications within the first year of initiation is associated with a significant reduction in fracture rates, [11] with up to a 60% reduction in hip fracture rates [14,15]. However, while there is consistent evidence that better medication compliance reduces fracture risk; the effect estimates reported are inconsistent.

One explanation for the inconsistent results may be differences in data source availability and analytic approaches. Pharmacy and medical claims data are the most commonly used data sources to estimate measures of medication compliance and health outcomes. While pharmacy data are considered reliable for exposure classification, we previously identified misclassification in the days supply reporting for extended dose osteoporosis medications that underestimated drug adherence, particularly in nursing home or long-term care (LTC) patients where compliance was underestimated by >25% [16,17]. Moreover, the risk for fracture, particularly hip fractures, is substantially higher among LTC patients when compared to community-dwelling patients [18]. Thus, with the increased fracture risk in LTC, failure to account for the differential exposure misclassification by site of patient residence may bias estimates of drug effects.

Thus, the objective of this manuscript was to investigate the impact of exposure misclassification on estimates of adherence to osteoporosis therapy when examining the relationship between compliance to anti-osteoporosis pharmacotherapy and hip fracture prevention.

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Methods

Data source

We used Ontario healthcare claims data (medical and pharmacy) to identify all new users of oral bisphosphonates. In Canada, all medical services are provided through a universal healthcare insurance, and all Ontario residents aged 65 or more years receive full coverage for all prescriptions listed on the Ontario Drug Benefit (ODB) formulary. During the study observation, all oral bisphosphonates were listed on the formulary without restriction, thus permitting complete drug coverage.

The ODB database includes detailed information about each prescription dispensed to patients residing in community or nursing homes (LTC). This information, recorded by the pharmacy technician or pharmacist, includes the patient identifier, prescription date, drug identification number, dose, quantity supplied, days supply (i.e., estimate of prescription duration), and a flag indicating patient residence (community or LTC). All fields are mandatory, pharmacy reimbursement is determined based on the quantity of drug dispensed and the drug identification number, while early or late refills are identified using the days supply values.

Study cohort

We utilized a previously identified cohort of new oral bisphosphonate users aged 66 or more years in Ontario, Canada (April 2001–March 2010) [17]. The index date for cohort entry was the first dispensing for an eligible oral bisphosphonate: alendronate (10 mg and 70 mg), etidronate (400 mg etidronate and 500 mg calcium), or risedronate (5 mg, 35 mg, and 150 mg). New users of oral bisphosphonates were identified using pharmacy claims and defined as having no use of any osteoporosis medication (bisphosphonate, calcitonin, denosumab, raloxifene) in the year prior to the index date. To examine the effect of compliance on hip fracture, we excluded patients with a diagnosis for a condition that may impact bone quality and fracture risk [17].

Exposure measurement

We defined compliance to therapy as the proportion of days covered (PDC), [6] which was identified during a one-year ascertainment period that followed index date (Figure 1). PDC was calculated as the total number of days supplied in the one-year ascertainment, divided by the number of days in the ascertainment period (365-days maximum), and capped at 100% [6]. Since medications dispensed during inpatient hospitalizations are not captured in Ontario pharmacy data, we deducted hospitalization days from the denominator of compliance and from the total gap length when measuring persistence [19]. Early refills of the same drug and dose was considered additive (cumulative use), while a switch between drugs or dosing regimens was considered a complete switch, and no overlap in days supply was granted.

Outcomes

Hip fractures were defined using validated diagnostic codes, with an estimated sensitivity and specific >90% [20]. Follow-up to identify fractures began one-year following the index date, and patient observation time ended at the first of: patient death, hip fracture, or end of the one-year follow-up.

Covariates

Patient demographics were determined on the date of the index prescription and health and medication related variables were identified in the year prior to the index date. We considered covariates that were related to hip fracture risk. These included demographic characteristics (e.g., age group, sex), osteoporosis related (e.g., prior fracture, osteoporosis diagnosis), disease comorbidities (e.g., diabetes, falls history, inflammatory arthritis), drug use (e.g., benzodiazepines, corticosteroids, narcotics), and indicators of health service utilization (e.g., prior hospitalizations). Additionally, we included variables that indicate health promotion (e.g., mammography or prostate exams, vaccinations) [12,21]. Hip fractures occurring during the one-year ascertainment period were included as a covariate in the outcome model.

Data cleaning

A complete description of data cleaning strategies has been described previously, including example data imputation scenarios [17]. In brief, we identified days supply values that did not match dose-specific expected values (e.g., 1 day supply for a monthly medication), and developed data cleaning algorithms to impute values that better reflected real-world utilization based on the medication, dose, quantity dispensed, and refill patterns (e.g., impute 30-days when 1-day observed for monthly medication) [17]. For example, if a 1-day supply was identified for a monthly medication a 30-day supply was imputed as the cleaned value. Data imputation was done in 10% of community prescription records and 41% of LTC prescription records [16,17]. Duplicate records were also removed prior to data analysis [17].

Statistical analysis

PDC was calculated using the two measures of days supply (observed and cleaned), [17] and was categorized into five groups: <20%, 20-39%, 40-59%, 60-79%, and ≥ 80%. In a secondary analysis, compliance was included as a dichotomous variable (PDC<80% and PDC ≥ 80%) and as a continuous variable.

Patient characteristics (demographic, comorbidities, health services use, and drug utilization) were summarized using means or proportions, as appropriate. Hip fracture rates were expressed as the number of events per 100 person-years. Cox proportional hazard models were used to compare event rates between compliance groups (<20% as referent), adjusting for covariates. A variable for calendar time (month and year) of the index prescription was included to adjust for trends in prescribing. We tested proportional hazard assumptions by including an interaction term between exposure and the log of time. No violations of the proportional hazard assumptions were identified. Analyses were calculated overall and separately for patients in community or LTC residence. All analyses were completed using SAS/STAT® software version 9.3 (SAS Institute, Inc., Cary, North Carolina) [22].

Results

We identified 279,343 eligible new users of oral bisphosphonates (n = 11,924 in LTC) (Figure 2). Following data cleaning, more patients were categorized as having high PDC (PDC ≥ 80%), yet little differences in patient characteristics across PDC categories were identified when using the observed or cleaned PDC (Table 1a and 1b). Compared to community-dwelling patients, LTC patients were older and had higher prevalence of comorbidities, drug utilization and prior fractures. Yet, they were less likely to have had a prior bone mineral density test, osteoporosis diagnosis or health promotion service.

We identified 254 hip fractures among LTC patients (incidence rate = 2.40 fractures per 100 person-years), in comparison to 2,703 hip fractures among community-dwelling patients (incidence rate = 1.03 fractures per 100 person-years). Changes in fracture rates across PDC groups following data cleaning are presented in Table 2. We report on

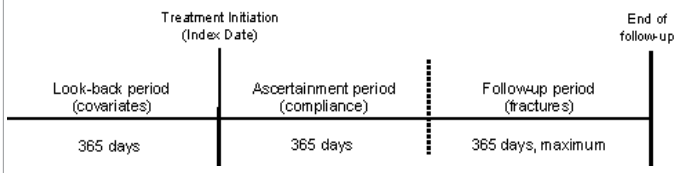
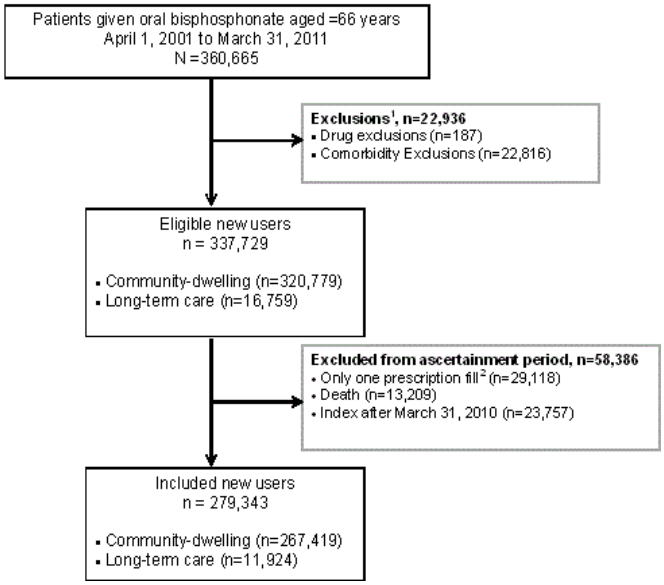


Figure depicts the cohort study design used to examine the relationship between osteoporosis medication compliance and fracture risk. All patients had a one-year look-back from index date (first dispensing of oral bisphosphonate after age 66) to identify baseline covariates. A one-year ascertainment was used following index date to identify and measure compliance using the proportion of days covered. Following the ascertainment period, all patients were followed for a maximum of one-year to identify hip fracture outcomes.

*Treatment initiation identified as first date of bisphosphonate dispensing. Fracture outcomes occurring during the ascertainment period were included as a covariate in the multivariate Cox proportional hazard mode. Compliance estimated using the proportion of days covered (PDC), adjusting for number of days in hospital = total days supply/(total number of days evaluated - number of days in hospital); capped at 1.0. Follow-up to identify hip fracture outcomes was a maximum of 365-days from the end of the ascertainment period, censored on the first date of death, hip fracture, or end of one-year observation.

Figure 1: Study Design.



[1]Exclusion criteria included diagnosis of celiac disease, Cushing syndrome, hypercalcemia, hyperparathyroidism, malignant neoplasm, osteomalacia, osteoporosis, Paget's disease, organ transplant, renal impairment or dialysis. Patients were further excluded if receiving clondronate or pamidronate, or men receiving estrogen therapy [17].

[2]Patients excluded if only one prescription during 365-day ascertainment period.

Figure 2: Study three flow diagram of cohort identification, April 2001-March 2011.

the adjusted hazard ratios (*unadjusted Cox proportional hazard results provided in in Appendix 1*). Notable differences in hazard ratio estimates were observed following data cleaning among patients in LTC. Using the observed PDC we identified that intermediate compliance (40-59% PDC) was associated with a statistically significant reduction in hip fracture rate ($HR_{observed}$ = 0.42, 95% CI = 0.20–0.92), while high compliance (PDC ≥ 80%) was associated with a non-significant 1% ($HR_{observed}$ = 0.99, 95% CI = 0.75–1.31) reduction in hip fracture rate. Conversely, the cleaned analysis identified only high compliance was associated with a significant reduction in hip fracture risk ($HR_{cleaned}$ = 0.65, 95% CI = 0.46–0.91). We observed similar results whether PDC was a dichotomous or continuous variable in the adjusted models.

Following data cleaning we identified that of the majority of patients in LTC were categorized in the high compliance (n = 9,176) or low compliance (n = 1,313) groups, with few in the moderate compliance categories (20% to 79%). Similarly, only 33 hip fractures were identified among patients in the moderate compliance categories. This resulted in some instability in estimates of drug effectiveness in these categories, with wide confidence intervals.

Among community-dwelling patients, we identified that higher compliance reduced the risk for hip fracture. Using the observed and cleaned PDC, we identified that high compliance was associated with a 31% ($HR_{observed}$ = 0.69, 95% CI = 0.60–0.78) and 34% ($HR_{cleaned}$ = 0.66, 95% CI = 0.56–0.76) reduction in hip fracture rate, respectively. Little difference in HR estimates was apparent between the observed and cleaned analysis when PDC was included as a dichotomous or continuous variable.

In the observed PDC analysis, combining LTC and community-dwelling patients resulted in an underestimation of the association between compliance and risk ($HR_{observed}$ = 0.75, 95% CI = 0.67–0.84). The cleaned analysis provided estimates more similar to those identified among community-dwelling patients ($HR_{cleaned}$ = 0.66, 95% CI = 0.57–0.75). Results were similar for dichotomous and continuous measures of PDC.

Discussion

Our results illustrate the potential influence of exposure misclassification in studies of osteoporosis drug effectiveness. In our study of Ontario seniors, misclassification of days supply values in pharmacy claims data resulted in an underestimation of the effect of drug compliance on fracture risk reduction, with the greatest influence seen in LTC. It is comforting to see minimal misclassification (<10%) and a minimal effect on drug effectiveness in the community setting, as this is where the majority of patients reside. However, while LTC patients represent only 5% of the study sample, combining these patients with community-dwelling patients may lead to biased estimates of drug benefit when using the observed days supply values to calculate PDC. The patients in LTC are sicker and more likely to have the outcome of interest. As we have shown in our findings, these patients were also more likely to be classified as non-compliant to their medications. Thus, our findings highlight the importance of data cleaning to correct for exposure misclassification.

These results build upon our previous work identifying the potential for days supply misclassification to underestimate medication compliance, [17] yet further add to the literature by providing a real-world application. In the area of osteoporosis pharmacotherapy, variation in risk estimates have made estimating the true relationship between bisphosphonate compliance and fracture risk reduction challenging [11,22]. While there are a number of factors that may influence the relationship between medication compliance and health outcomes, our results suggest that the accuracy of exposure and patient residence classification may play an important role.

We were able to stratify our results by residence status and as a result highlighted some key differences in both potential exposure misclassification and benefit of medication compliance, and we believe these warrant additional discussion as LTC patients are often not stratified from their community-dwelling counterparts in studies of drug outcomes. Compared to community-dwelling patients, patients

	Observed days supply					Cleaned days supply				
Compliance (PDC), %	<20	20-39	40-49	50-79	≥80	<20	20-39	40-49	50-79	≥80
N	17,535	32,271	27,742	34,005	155,866	10,985	28,937	25,552	34,491	167,454
Demographics										
Female	81.5	81.6	81.7	82.1	81.9	81.9	81.8	81.0	82.0	81.9
Age, mean (SD)	75.8 (7.2)	74.9 (6.7)	74.9 (6.7)	74.7 (6.6)	75.0 (6.6)	76.3 (7.3)	74.9 (6.6)	74.9 (6.7)	74.6 (6.6)	75.0 (6.6)
Age category										
65-69	24.6	26.7	26.8	28.1	25.6	23.2	26.9	27.0	28.3	25.6
70-74	23.5	25.6	25.7	25.9	26.3	22.0	25.6	25.6	26.1	26.3
75-79	21.2	22.4	22.1	22.0	23.0	21.3	22.3	22.3	21.9	22.9
80-84	17.3	15.8	15.5	15.1	15.6	18.4	15.8	15.4	15.1	15.6
85+	13.4	9.5	9.9	9.0	9.4	15.2	9.3	9.6	8.7	9.6
Osteoporosis Variables										
DXA test	63.2	67.1	66.6	69.2	70.6	62.5	66.6	65.6	69.2	70.5
Previous fracture	10.3	7.2	7.4	7.0	8.1	11.5	7.1	7.2	6.8	8.1
Osteoporosis diagnosis	36.2	37.5	37.8	39.5	41.0	36.9	37.4	37.4	39.3	40.8
Health Services Use										
Hospitalization	16.9	13.1	13.5	12.8	14.0	18.7	12.8	13.1	12.5	14.1
Physician visits, mean (SD)	10.7 (8.0)	10.4 (7.8)	10.4 (7.7)	10.3 (7.6)	10.3 (7.4)	10.7 (8.1)	10.5 (7.9)	10.4 (7.8)	10.3 (7.6)	10.3 (7.4)
Colonoscopy	12.5	13.1	13.0	14.2	14.2	12.6	13.1	13.0	14.3	15.0
Mammography[1]	19.8	22.5	22.4	23.9	23.9	19.0	22.6	22.2	23.7	23.9
Prostate exam[1]	1.6	1.3	1.4	1.4	1.4	2.3	1.4	1.3	1.5	1.5
Vaccination	6.0	5.7	5.9	5.7	5.7	5.9	5.7	5.8	5.7	5.4
Comorbidities										
Asthma/COPD/Emphysema	8.0	7.3	7.4	6.9	6.6	8.1	7.3	7.4	6.8	6.7
Alzheimer's/other dementia	7.3	4.0	4.3	4.0	4.6	7.7	3.6	4.0	3.7	4.8
Depression	20.8	19.1	19.2	18.0	17.5	21.2	19.3	19.1	18.1	17.6
Diabetes	10.9	10.3	10.8	10.1	10.0	11.1	10.0	10.6	10.2	10.1
Falls/syncope/neurological	6.2	3.3	3.5	3.1	4.0	7.5	3.2	3.3	3.0	4.1
Hyperparathyroidism	0.9	0.8	0.8	0.8	0.8	0.8	0.9	0.8	0.8	0.8
Inflammatory arthritis	5.6	5.0	5.3	5.2	5.1	5.8	5.2	5.2	5.1	5.1
Inflammatory bowel disease	0.5	0.5	0.4	0.4	0.4	0.5	0.5	0.4	0.4	0.4
Liver disease	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1
Parkinson's disease	1.7	1.4	1.4	1.4	1.5	1.9	1.3	1.3	1.3	1.5
Stroke	4.1	3.3	3.3	3.3	3.4	4.3	3.2	3.1	3.2	3.5
Drug Utilization										
No. drug classes, mean (SD)	7.7 (5.7)	7.1 (5.4)	7.2 (5.4)	7.0 (5.2)	7.0 (5.1)	7.6 (5.7)	7.1 (5.4)	7.2 (5.4)	6.9 (5.2)	7.0 (5.2)
Angiotensin II antagonist	8.2	7.3	7.4	7.6	8.0	9.0	7.5	7.4	7.4	8.0
Anticonvulsants/Epileptic	1.9	2.0	1.8	1.8	1.9	1.8	1.8	1.7	1.8	1.9
Aromatase inhibitors[1]	0.8	0.7	0.8	0.8	1.1	1.8	0.7	0.8	0.8	1.0
Benzodiazepines	24.4	23.1	22.7	21.7	21.0	25.0	23.3	22.6	21.6	21.2
Beta-blockers	12.6	12.5	12.7	12.5	12.7	12.5	12.5	12.4	12.4	12.7
Corticosteroids	14.1	13.5	14.3	13.5	13.1	13.8	13.9	14.1	13.3	13.2
Gastroprotective Agents	33.0	30.9	30.7	29.4	39.5	33.6	30.9	30.6	29.4	29.7
Glitazones	1.0	0.8	0.9	1.0	0.9	1.1	0.9	0.9	1.0	0.9
Narcotics	29.9	28.0	27.8	27.0	26.2	30.5	28.0	28.0	27.0	26.3
Nitrates	9.1	8.1	8.9	7.9	8.2	8.9	8.0	8.5	7.9	8.3
Non-SSRIs	12.6	10.2	10.3	10.1	10.0	12.5	10.0	10.2	10.0	10.2
NSAIDs	30.4	31.0	32.2	30.4	29.3	28.2	30.4	31.6	30.7	29.7
SSRIs	12.3	10.1	10.6	10.2	9.6	12.5	9.9	10.4	10.2	9.8
Statins	32.2	31.0	31.8	32.8	34.3	32.9	30.5	31.4	32.6	34.3
Thiazide diuretics	25.5	24.7	25.3	26.4	27.0	26.1	24.5	25.1	26.2	26.9
Thyroid medications	16.3	15.2	15.3	15.7	16.4	16.9	15.0	15.1	15.5	16.4

[1]Proportions for aromatase inhibitors and mammography testing among females, and proportion for prostate exam among males.
COPD: Chronic Obstructive Pulmonary Disease; SSRI: Selective Serotonin Reuptake Inhibitor; NSAID: Non-Steroidal Anti-Inflammatory Drug; PDC: Proportion of Days Covered

Table 1a: Demographic characteristics among patients residing in community (N = 267,419), stratified by observed and cleaned compliance groups.

	Observed Days Supply					Cleaned Days Supply				
Compliance (PDC), %	<20	20-39	40-49	50-79	≥80	<20	20-39	40-49	50-79	≥80
N	3,773	939	766	640	5,806	1,313	485	392	558	9,176
Demographics										
Female	81.8	83.7	80.8	84.8	83.5	82.7	83.9	77.8	83.3	83.0
Age, mean (SD)	84.3 (6.9)	84.1 (7.3)	83.4 (7.4)	83.8 (7.3)	83.9 (7.1)	84.1 (6.9)	84.5 (6.9)	84.0 (6.8)	84.0 (7.3)	83.9 (7.1)
Age category										
65-69	3.3	3.2	5.0	4.5	3.5	3.6	2.7	2.3	5.9	3.5
70-74	5.9	8.2	7.6	6.7	7.1	5.9	6.2	7.4	5.7	7.0
75-79	14.0	13.8	15.4	15.0	15.0	14.9	14.6	14.5	13.3	14.7
80-84	24.7	25.1	26.8	26.1	25.4	24.8	24.5	26.8	26.2	25.3
85+	53.7	52.0	49.3	50.2	51.0	52.8	52.9	49.7	53.1	49.5
Osteoporosis Variables										
DXA test	10.4	12.0	10.4	12.2	12.3	11.3	11.1	9.4	12.4	11.6
Previous fracture	35.3	33.4	28.2	34.8	32.9	34.7	38.1	34.4	33.6	33.2
Osteoporosis diagnosis	14.3	17.7	12.1	17.8	14.9	14.9	18.6	11.5	14.7	14.9
Health Services Use										
Hospitalization	52.1	50.5	46.9	54.4	51.1	52.7	53.0	55.1	50.9	50.8
Physician visits, mean (SD)	6.2 (7.1)	6.6 (7.6)	6.4 (7.2)	7.0 (7.3)	6.5 (7.1)	6.9 (7.4)	7.1 (8.2)	6.8 (7.4)	6.9 (7.3)	6.3 (7.0)
Colonoscopy	5.5	5.2	5.4	5.6	5.5	5.9	6.0	5.9	4.5	5.4
Mammography[1]	2.2	1.5	2.3	2.8	2.1	2.2	1.7	1.3	2.4	2.1
Prostate exam[1]	0.6	0.7	0.0	2.1	1.3	0.0	0.0	0.0	0.0	1.2
Vaccination	10.8	12.0	11.0	10.9	11.2	10.9	11.8	12.5	11.3	3.5
Comorbidities										
Asthma/COPD/Emphysema	10.8	12.0	11.0	10.9	11.2	10.9	11.8	12.5	11.3	11.0
Alzheimer's/other dementia	65.9	60.8	59.0	62.3	60.4	65.0	55.1	59.9	65.6	62.1
Depression	28.8	31.5	31.2	31.3	30.5	28.6	30.1	29.1	29.4	30.4
Diabetes	13.7	13.0	13.2	9.5	12.7	14.4	12.2	16.1	9.1	12.8
Falls/syncope/neurological	31.1	23.5	21.5	28.8	25.3	30.3	28.9	29.1	26.3	26.3
Hyperparathyroidism	0.3	1.2	1.0	0.6	0.7	0.2	0.4	0.5	0.5	0.7
Inflammatory arthritis	3.9	4.8	3.9	4.8	4.4	4.5	4.5	4.6	3.4	4.3
Inflammatory bowel disease	0.5	0.3	0.7	1.1	0.5	0.3	0.6	0.8	0.7	0.5
Liver disease	0.4	0.1	0.4	0.3	0.2	0.7	0.0	0.8	0.5	0.2
Parkinson's disease	6.7	6.3	7.2	7.0	7.8	6.5	5.8	8.7	7.9	7.4
Stroke	16.8	18.2	19.1	15.5	16.2	17.8	15.7	17.1	16.5	16.6
Drug Utilization										
No. drug classes, mean (SD)	11.2 (6.3)	10.4 (6.0)	10.9 (6.0)	10.6 (6.0)	10.8 (6.1)	11.0 (6.3)	10.7 (6.2)	11.4 (6.4)	10.8 (5.6)	10.9 (6.1)
Angiotensin II antagonist	6.2	5.5	3.7	4.1	5.3	6.3	5.8	5.4	3.8	5.4
Anticonvulsants/Epileptic	7.6	8.0	7.7	7.2	7.6	8.0	8.0	5.4	7.7	7.6
Aromatase inhibitors[1]	0.5	0.6	0.5	0.4	0.4	0.8	0.2	0.7	0.6	0.4
Benzodiazepines	38.6	38.2	40.5	42.2	41.3	38.6	34.0	39.8	42.8	40.6
Beta-blockers	13.8	11.4	14.8	12.5	13.3	13.8	12.2	16.6	12.0	13.3
Corticosteroids	16.5	17.0	19.7	16.6	16.8	14.9	17.1	17.9	18.1	17.0
Gastroprotective Agents	38.7	38.1	41.9	37.8	38.5	38.0	37.5	39.0	40.4	38.8
Glitazones	0.9	1.0	0.3	0.5	0.6	1.1	0.8	1.0	0.4	0.6
Narcotics	42.3	40.3	40.9	37.3	40.3	43.6	42.9	40.6	40.1	40.4
Nitrates	16.2	16.2	18.0	14.8	17.9	15.6	19.4	18.6	14.9	17.2
Non-SSRIs	45.6	40.4	42.6	44.1	43.6	42.7	39.8	46.9	47.1	44.0
NSAIDs	25.0	26.0	24.0	22.8	25.0	23.5	25.8	20.9	22.2	25.3
SSRIs	34.7	30.1	31.5	31.4	34.4	32.2	28.0	34.2	31.9	34.5
Statins	23.0	17.1	18.3	18.6	19.8	23.2	19.2	22.2	18.6	20.2
Thiazide diuretics	22.3	19.3	22.5	24.4	21.9	25.6	22.3	21.2	21.7	21.5
Thyroid medications	21.7	20.3	19.8	20.6	20.8	19.6	20.2	19.4	18.8	21.4

[1]Proportions for aromatase inhibitors and mammography testing among females, and proportion for prostate exam among males.
COPD: Chronic Obstructive Pulmonary Disease; SSRI: Selective Serotonin Reuptake Inhibitor; NSAID: Non-Steroidal Anti-Inflammatory Drug
PDC: Proportion of Days Covered.

Table 1b: Demographic characteristics among patients residing in long-term care (N = 11,924), stratified by observed and cleaned compliance groups.

	Observed Days Supply					Cleaned Days Supply				
	N	Events (n)	Rate[1]	HR	95% CI	N	Events (n)	Rate[1]	HR	95% CI
Long Term Care										
PDC Groups										
<20%	3,773	87	2.61	1.00	Referent	1,313	40	3.44	1.00	Referent
20-39%	939	18	2.18	0.85	0.51–1.42	485	18	4.28	1.22	0.70–2.14
40-59%	766	8	1.16	0.42	0.20–0.92	392	6	1.74	0.44	0.17–1.11
60-79%	640	10	1.77	0.69	0.36–1.33	558	9	1.87	0.55	0.26–1.14
≥80%	5,806	131	2.54	0.99	0.75–1.31	9,176	181	2.22	0.65	0.46–0.91
PDC Groups										
0-79%	6,118	123	2.27	1.00	Referent	2,748	73	3.03	1.00	Referent
80-100%	5,806	131	2.54	1.14	0.89–1.46	9,176	181	2.22	0.74	0.56–0.98
Continuous PDC										
Total	11,924	254	2.40	0.95	0.70–1.29	11,924	254	2.40	0.61	0.43–0.85
Community										
PDC Groups										
<20%	17,494	276	1.64	1.00	Referent	10,952	192	1.82	1.00	Referent
20-39%	32,105	378	1.19	0.87	0.73–1.00	28,750	361	1.28	0.89	0.74–1.01
40-59%	27,828	277	1.02	0.74	0.62–0.87	25,676	254	1.01	0.71	0.57–0.83
60-79%	33,741	312	0.94	0.71	0.59–0.82	34,196	317	0.94	0.68	0.56–0.80
≥80%	156,251	1,460	0.95	0.69	0.60–0.78	167,845	1,579	0.96	0.66	0.56–0.76
PDC Groups										
0-79%	111,168	1,243	1.16	1.00	Referent	99,574	1,124	1.17	1.00	Referent
80-100%	156,251	1,460	0.95	0.85	0.79–0.91	167,845	1,579	0.96	0.83	0.77–0.90
Continuous PDC										
Total	267,419	2,703	1.03	0.70	0.63–0.79	267,419	2,703	1.03	0.67	0.59–0.75
All Patients										
PDC Groups										
<20%	21,267	363	1.81	1.00	Referent	12,265	232	1.99	1.00	Referent
20-39%	33,044	396	1.21	0.92	0.80–1.07	29,235	379	1.25	0.90	0.76–1.06
40-59%	28,594	285	1.01	0.77	0.66–0.91	26,068	260	1.02	0.70	0.58–0.83
60-79%	34,381	322	0.99	0.75	0.65–0.88	34,754	326	0.99	0.68	0.57–0.80
≥80%	162,057	1,591	1.00	0.75	0.67–0.84	177,021	1,760	1.02	0.66	0.57–0.75
PDC Groups										
0-79%	117,286	1,366	1.21	1.00	Referent	102,322	1,197	1.21	1.00	Referent
80-100%	162,057	1,591	1.00	0.87	0.81–0.94	177,021	1,760	1.02	0.83	0.77–0.89
Continuous PDC										
Total	279,343	2,957	1.06	0.74	0.67–0.83	279,343	2,957	1.06	0.66	0.59–0.74

[1]Multivariate model adjusted for all variables listed in Table 1
[2]Hip fracture rate/100 person-years of observation
HR: Hazard Ratio; CI: Confidence Interval; PDC: Proportion of Days Covered

Table 2: Adjusted Cox proportional hazard estimates, stratified by observed and cleaned days supply values.

in LTC were older, had more comorbidities increasing risk for fracture, had higher overall drug utilization, and a higher rate of prior hospitalization. It is also important to recognize the difference between the reasons for non-adherence among community-dwelling patients in comparison to LTC patients [23]. The decision to discontinue, or miss doses, among community-dwelling patients is likely an individual decision, except in some cases of physician directed discontinuation. Conversely, in the LTC setting such decisions would often be nurse, or family member, directed.

Finally, in regards to the potential for exposure misclassification, there are important differences in the billing restrictions placed upon medications dispensed to community-dwelling patients, as compared to LTC patients [24, 25]. For example, the capitated reimbursement in community pharmacies, that restricts pharmacies to two dispensing fees per month for a given medication, is not applied to LTC dispensed medications [24]. Thus, full reimbursement of frequent (e.g., daily or weekly) dispensing is possible to pharmacies with LTC contracts, and may partially explain the tendency for the short cycle dispensing observed. This may begin to shed some light on the higher proportion of misclassified days supply values identified in LTC compared to community in our analysis. It is important to understand why inaccurate days supply reporting may occur, particularly in the LTC setting. We expect that there may be a number of reasons that may influence data entry, including structure and process level factors that may facilitate data entry efficiency. For example, frequent dispensing may result from the billing structure in LTC pharmacies and as a means to avoid medication errors among patients with complex care. However, a thoughtful investigation is required to best inform future educational strategies aimed towards pharmacies to emphasize the importance of accurate data entry.

While our study has several important methodological and clinical messages, some limitations merit emphasis. First, we did not complete a validation study to confirm imputed days supply values with prescriptions, however, osteoporosis medications have fixed dosing intervals, and therefore the logical days supply can be inferred. In a sensitivity analysis (data not shown), we imputed a corrected days supply by simply multiplying the quantity dispensed by expected dose interval (e.g., 7 for weekly medications). While minimal differences in the final HR from our primary analysis were identified, we identified highly skewed days supply values (i.e., range: 0.1-16,000) suggesting additional errors in the quantity reported. Thus, we believe a more detailed approach is warranted; yet we recognize that additional validation may be required, particularly for medications with more complex dosing intervals.

Second, we used medical claims data to identify hip fractures and estimate confounders, and therefore there is the potential for missing data. While immeasurable confounders are a limitation when using claims data, the aim of this study was to examine the methodological impact of exposure misclassification in the days supply values on estimates of fracture risk. Thus, any unmeasured confounders would be constant in both the observed and cleaned days supply analyses. Similarly, in using Ontario pharmacy claims data we were unable to identify drug utilization prior to age 65. While we applied a one-year look-back period to identify new users, it is possible that some new users at age 66 had received osteoporosis therapy prior to age 65. Another limitation to our study was that we identified fewer outcomes and person time in the intermediate PDC categories in LTC settings, thereby making estimates unstable. We believe this may be an indicator of prescribing practices in LTC facilities, where physicians may make fewer changes to medication use during a patient's stay. Thus, we would expect early discontinuation (PDC<20% due to medication complications) or continued use for the duration of their time in LTC (PDC ≥ 80%), and this pattern was reflected following data cleaning.

Despite the noted limitations, our study had a number of strengths. The selection of osteoporosis pharmacotherapy and hip fracture outcome permitted an examination of the impact of exposure misclassification on estimates of bisphosphonate effectiveness. Oral bisphosphonates have scheduled dosing intervals, and we were previously able to identify the influence of days supply cleaning on quantifying compliance in this population of Ontario seniors [17]. Further, hip fractures are the most serious consequence of osteoporosis and are well captured in administrative data, thereby reducing the potential for outcome misclassification [20]. Second, we stratified by site of patient residence. Few studies have examined the association between compliance and fracture risk in community and LTC separately. We identified that patients' in LTC facilities were older, with more comorbidities and drug utilization, and had a fracture risk that was more than double that of community-dwelling patients. With little available research on drug compliance and drug effectiveness in LTC facilities our results provide some evidence supporting the need for high medication compliance to osteoporosis pharmacotherapy in this patient population. While patients in LTC are expected to have poorer outcomes, we observed an increased benefit of bisphosphonate compliance, following data cleaning that was similar to community-dwelling patients. This may have important quality of life benefits for these patients, and therefore support the need for further investigation into the use of oral bisphosphonates in LTC settings.

From a methodological perspective, our study has some important strength. To our knowledge, we are the first to report the potential influence of cleaning days supply values on exposure misclassification and estimates of drug effectiveness. We found that data cleaning, particularly in LTC, produced estimates of drug effectiveness that are more consistent with results from clinical trials, thus providing some comfort to the accuracy of our data cleaning algorithm [25]. Second, our analysis was strengthened by the inclusion of three PDC definitions that identified how the definition of exposure can influence estimates of drug effects. This is unique to our study and provides some insight to the variation in estimates identified in the literature.

Conclusions

Using osteoporosis pharmacotherapy and hip fractures as the case example, the current manuscript highlights several of these methodological (exposure classification) and clinical (compliance benefit) implications. To our knowledge, no study to date has examined the impact of misclassification in a real-world drug effectiveness example. Our results add to the growing body of literature advancing methodological practice to address and overcome the inherent challenges when utilizing large administrative claims data to study patterns of drug utilization and examine drug safety and effectiveness in real-world databases [17,26,27].

We believe additional research is warranted to examine the impact of exposure misclassification in days supply values in safety research, and in other disease areas with extended-dose medications, before strong conclusions are drawn. Our results highlight the potential influence of misclassified days supply and serve as a signal to encourage researchers to examine and report on any data cleaning strategies. We posit that greater accuracy in exposure measurement and transparency in methodological reporting will lead to improved estimates of drug effectiveness used to inform policy decisions [28].

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