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Measuring drug exposure: concordance between defined daily dose and days' supply depended on drug class.

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Abstract

Objective—To determine the concordance between two methods to measure drug exposure duration from pharmacy claims data.

Study design and setting—We conducted a cohort study using 2002–2007 US Medicaid data. Initiators of eight drug groups were identified: statins, metformin, atypical antipsychotics, warfarin, proton pump inhibitors (PPIs), angiotensin converting enzyme (ACE)-inhibitors, non-steroidal anti-inflammatory drugs (ns-NSAIDs) and coxibs. For each patient, we calculated two measures of exposure duration using 1) observed days' supply available in US pharmacy claims and 2) the World Health Organisation Daily Defined Doses (DDD) methodology. We used Wilcoxon signed rank tests to compare medians and Spearman correlations to assess correlation between the two measures.

Results—Cohort sizes ranged from 143,885 warfarin users to >3,000,000 ns-NSAID users. Similar median exposure durations were observed for ACE-inhibitors (70days vs. 75days), PPIs (44days vs. 45days) and coxibs (44days vs. 45days). The DDD method overestimated exposure duration for ns-NSAIDs and underestimated for the remaining drug groups, relative to days' supply. Spearman correlation coefficients ranged from 0.2–0.8.

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Conclusion—Using DDDs to estimate drug exposure duration can result in misclassification. The magnitude of this misclassification might depend on doses used which can vary according to factors such as local prescribing practices, renal function and age.

Keywords

Pharmacoepidemiology; Bias(Epidemiology); Prescription drugs/supply; Drug Exposure; Medicaid; Daily Defined Dose

Introduction

Pharmacoepidemiological studies often rely on administrative pharmacy claims data to measure drug exposure. [1–4] Dispensing data can be used to estimate the number of days of therapy, and therefore the number of days a patient is exposed to a drug. Such measurements are required for establishing temporal relationships between drugs and clinical events.

In the US, most pharmacy claims databases include a days' supply variable that provides a pharmacist-determined number of days that each prescription will last if used according to the prescribing instructions, which themselves are not included in pharmacy claims data. For example, if an individual is dispensed 30 pills and is instructed to take one per day, the estimated days' supply is 30. In a validation study of Medicaid data, the days' supply variable was found to accurately estimate exposure duration for drugs used in the treatment of HIV. [5] It can be reasonably expected that the days' supply can also accurately estimate exposure duration for other drugs with fixed prescribing instructions.

Databases outside of the US often do not include the days' supply variable. Instead, researchers often depend on other measures, such as those that use the minimum marketed dose (MMD) or converting text data on dosage to treatment days or the prescribed daily dose (PDD). [6, 7] The World Health Organisation's (WHO) Defined Daily Dose (DDD) methodology is the most frequently used approach when days' supply is unavailable.[8] The DDD is the assumed average maintenance dose for the main indication of a drug in adults. It is used as a standardised unit of measurement in drug utilisation studies, often expressed as number of DDDs per 1000 inhabitants per day.[8] In a comparison of the DDD with other measures such as the MMD and the PDD, Merlo *et al.* found that the DDD emerged as being the superior measure. [6]

Although not the intended purpose of the DDD, many studies in European databases and others around the world have used the DDD to estimate individual patients' exposure duration.[9–13] It is not known to what extent exposure duration assessed using the DDD methodology corresponds to duration assessed using days supply. We used a US Medicaid database to measure the concordance of the DDD and days' supply approaches across eight drug classes.

Methods

Ethics

This study was approved by the Brigham and Women's Hospital Institutional Review Board. Both written and oral consent requirements were waived because this was a secondary analysis of previously collected and anonymised data.

Data

We used US Medicaid pharmacy claims data for 48 states and the District of Columbia from 2002–2007. Medicaid is a state-based government-provided health insurance program for low income individuals, covering approximately 60 million Americans.[14] The Medicaid Analytic eXtract (MAX) data include information on drugs dispensed, dispensing date, strength, quantity and days' supply, as well as medical claims information. Data on DDDs were obtained from www.whocc.no/atc_ddd_index/. In some instances, the DDD for a drug may have changed during, or since, the study period. In all cases, we used the most up to date DDD available at the time of analysis.

Study Design, Patients and follow-up

We conducted a cohort study to assess the level of agreement between two methods for calculating duration of drug exposure in claims data. Patients were eligible for inclusion in the study if they were new users (no prior use in previous 6 months and had a minimum of 6 months of continuous prior enrolment in Medicaid) of solid oral dosage forms of one of the following eight drug groups: (1) angiotensin converting enzyme (ACE)-inhibitors; (2) statins; (3) metformin; (4) atypical antipsychotics; (5) warfarin; (6) proton pump inhibitors (PPIs); (7) non-selective non-steroidal anti-inflammatory drugs (ns-NSAIDs); (8) and coxibs. The new user design allowed estimation of duration of exposure from start of treatment, which is more difficult to assess in prevalent users because the starting point is not known.[15] These commonly used drugs and drug groups were chosen to reflect medications that are intended to be used both chronically and episodically, along with drugs such as warfarin that often involve frequent dose changes, as these factors may impact on the measurement of drug exposure duration.[5] We excluded combination drug products and drugs that had more than one DDD (e.g., ibuprofen). Patients who were dually enrolled in Medicare or had private health insurance were excluded.

Patients were followed starting on the date of their first prescription for a study drug until the first of the following: discontinuation of index medication, dispensing of another drug within the same therapeutic group, loss of eligibility or disenrollment, death, or the end of the study period. We defined discontinuation as a period of more than 14 days between the estimated end of a prescription and the date of dispensing of a subsequent prescription, if any. We chose a 14 day gap to allow for modest non-adherence while also attempting to balance the preservation of differences between the two approaches that would be obscured with a larger gap.

Exposure classification

Exposure duration was calculated in two ways. First, we used the observed days' supply variable to count days of continuous exposure to the index drug. The days supply variable is based on a pharmacist's estimate of the number of days that a prescription is expected to last if used according to the prescribing instructions. It is manually entered into the insurance claim at the time of dispensing. We bridged serial prescription dispensing if the date of each dispensing event was within the days' supply plus the 14-day gap.

The second method determined continuous exposure duration by counting the number of DDDs a patient received. The number of DDDs was calculated as: $(\text{strength of drug dispensed} \times \text{quantity dispensed}) \div \text{DDD}$ for that drug. For example, if a person received 112 pills of 500mg metformin, which has a DDD of 2000mg, the person received 28 DDDs (i.e., $[112 \times 500] \div 2000$). Thus, every patient in the cohort had two estimated treatment durations – one based on days' supply and the other based on DDDs.

Statistical analysis

We plotted and compared the distributions of the two measures of exposure duration. We calculated the median duration of exposure to each drug group for each method and compared the two measures using the Wilcoxon signed rank test, given the paired and non-normally distributed nature of the data. We determined the level of agreement between the two methods in three ways. First, for each individual we calculated the proportion of estimates that agreed completely ± 1 day since the DDD approach can result in non-integer estimates of exposure duration. Second, we calculated the proportion of estimates where the DDD method gave a higher estimate than the days' supply. Third, the proportion of estimates where the DDD method gave a lower estimate than the days' supply was assessed. We also created scatter plots to examine the correlation between the two measures and calculated the Spearman correlation coefficient to quantify the level of agreement between the two approaches.

Results

Across the eight drug groups, the number of individuals eligible for analyses ranged from 143,885 for warfarin to over 3,000,000 for ns-NSAIDs (Table 1). Each drug cohort was predominantly female, ranging from 54% in the atypical antipsychotic cohort to 74% in the ns-NSAIDs cohort. Mean age varied widely across the drug groups, ranging from 28 years in the atypical antipsychotic cohort to 48 years in the statin cohort.

The level of agreement between the two measures varied widely across the eight drug groups. Estimated median durations of exposure using the two approaches were similar for ACE-inhibitors (70 days [IQR 44–136] for days' supply and 75 days [IQR 35–170] for DDDs), PPIs (44 days [IQR 44–76] for days' supply and 45 days [IQR 45–80] for DDDs), and coxibs (44 days [IQR 42–66] for days' supply and 45 days [IQR 45–75] for DDDs; Figure 1). The DDD approach substantially underestimated the median exposure duration for statins, metformin, atypical antipsychotics, and warfarin and overestimated the exposure

duration for ns-NSAIDs. The Wilcoxon signed rank test indicated statistically significant differences across all eight drug groups owing to the large sample sizes.

In the PPI and coxib cohorts, 69% and 60% of the exposure duration estimates, respectively, were identical (Figure 2). Despite good agreement in median exposure duration between the two approaches in the ACE-inhibitor cohort, the proportion of identical estimates was only 35%, with roughly a third of DDD-based estimates larger than the days' supply estimates and a third smaller. The proportion of identical estimates was less than 20% in the metformin, atypical antipsychotic, warfarin, and ns-NSAID cohorts. The DDD underestimated the days' supply for more than 75% of patients in the metformin and atypical antipsychotic cohorts and overestimated for more than 75% of patients in the ns-NSAID cohort. The correlation coefficients between the estimated durations of exposure ranged from 0.2 for atypical antipsychotics to 0.8 for PPIs, coxibs, and ns-NSAIDs (Table 2).

Discussion

In this large cohort study that investigated the level of agreement between days' supply and DDD based methods for calculating exposure duration, we found high concordance between the methods in two (PPIs and coxibs) out of eight drug groups and good agreement in median estimated exposure duration for ACE-inhibitors. However, the DDD method usually underestimated duration of exposure, including in more than 75% of metformin and atypical antipsychotic initiators. The median estimated duration of exposure using the DDD method was 55% smaller than the median estimate using the days' supply for atypical antipsychotics.

Our findings have important implications for studies that rely on DDDs to estimate drug exposure. Inaccurate estimates of drug use duration can result in bias due to exposure misclassification in pharmacoepidemiologic studies. Imagine a hypothetical cohort in which 200 events occur over 1,000 exposed person-years and 100 events occur over 1,000 unexposed person-years, yielding a true incidence rate ratio of 2.00. If, as observed in atypical antipsychotics with the DDD approach, 55% of the exposed time was misclassified as unexposed time, we would observe 90 events among 450 exposed person-years and 210 events among 1,550 apparent unexposed person-years, yielding an observed incidence rate ratio of 1.48. The magnitude of bias due to exposure misclassification depends on a number of features of the study, including the study design and analysis approach and the relative amount of person time among exposure groups.

Several factors may explain the observed discrepancies between the two approaches. First, DDDs are an assumed average daily dose for a drug for its main indication in adults. They are assigned considering different doses used in different countries.[16] Thus, geographic variation in drug use, both in terms of dose, and indications for use, can limit the accuracy of DDDs in estimating exposure duration in certain countries or regions.[17] If higher doses of drugs, in general, are used in the US relative to the DDD, we would then expect the DDD methodology to overestimate days' supply. Future studies comparing DDDs dispensed in different countries could elucidate geographic differences in dosing. Further, DDDs change

over time to reflect changes in dosing practices e.g. the DDD for atorvastatin was changed from 10mg to 20mg in 2009. This affects the ability of the DDD method to reliably estimate exposure over time if some countries continue to use the lower dose.

The agreement we observed between the two methods in estimating duration of exposure to ACE-inhibitors, PPIs, and coxibs is likely because the DDDs for those drugs accurately reflect doses used in the US.[18–20] Indeed, for illustrative purposes, we examined average doses for the first prescription for these drugs in our cohort and found that they were often similar to the corresponding DDDs. For example, the DDD for lansoprazole, the most commonly used PPI in our study, is 30mg and the average daily starting dose for cohort members was 31mg. The DDD method underestimated exposure for statins, metformin, and atypical antipsychotics, likely because the average doses used in our study were smaller than the DDDs. For example, in the case of metformin, the average daily prescribed dose for the first prescription was 1000mg in our cohort, similar to a previous estimate in a Medicaid population[21], which contrasts with a DDD of 2000mg. Likewise, the mean starting doses for risperidone (1mg) and quetiapine (150mg) in the study cohort were much lower than their DDDs (5mg and 400mg, respectively). Initiators of risperidone and quetiapine made up 66% of all atypical antipsychotic initiators in our study cohort, explaining the overall underestimation.

The mean daily naproxen dose was greater than 1000mg in our study cohort, which is consistent with the literature[18] and more than twice the DDD of 500mg. As naproxen initiators comprised 75% of NSAID initiators in our study cohort, this likely explains why the estimated duration of exposure was longer with the DDD method.

To the best of our knowledge, this is the first study to assess the level of agreement between the days' supply variable and DDD methods of calculating drug exposure. A related study by Polk *et al.* examined the use of antibiotics in adult patients in US hospitals using DDDs and a measure of exposure referred to as 'days of therapy' (DOT).[22] One DOT was equal to each day that a patient was exposed to an antibiotic, regardless of strength or dosing regimen. The authors found that the mean value for the DDD method closely reflected the mean value for the DOT method. However, the authors explain that this was a function of the DDD method overestimating exposure for some antibiotics, and vastly underestimating for other antibiotics. This supports our findings that DDDs may not provide accurate estimation of exposure duration for drugs used with varying dosing schedules or doses that do not exactly match the DDD. Our study also extends the work of Polk *et al.* by including a variety of drugs intended to be used both chronically and episodically disease. Further, our study focuses on the relation between the DDD and 'days supply', which is the most commonly used method for determining drug exposure duration in pharmacoepidemiological studies.

Our study has several limitations. First, records of dispensing do not assure actual drug consumption and, therefore, are a proxy for drug exposure, although this impacts both measures of exposure duration.[23] Second, while we used days' supply as the reference standard, it should not be considered a perfect gold standard. Its use has been validated in anti-retroviral medicines, with results that extend to other chronic disease medicines with a fixed dose, but not drugs that are used on an as needed basis.[5] Third, as noted above, our

results in a US Medicaid population might not generalize to other populations, including older populations and other populations that require dose adjustments, such as those with renal impairment. Our population of US Medicaid beneficiaries also included children, who might require lower doses than the average adult dose. DDDs are likely to underestimate days' supply for children and other patients who use less than the average adult dose. However, most of the drugs that we studied, except perhaps for ns-NSAIDs, are almost exclusively used in adults. Fourth, the discontinuation gap of 14 days is smaller than that used in some pharmacoepidemiologic studies. However, we chose a conservative approach to avoid obscuring true differences between the two methods. Fifth, some drugs are used at different doses in different conditions. For example, lower doses of ACE-inhibitors are used in hypertension than in chronic heart failure. Since we focused on drugs with a single DDD, we considered all initiators of these drugs and did not attempt to restrict to patients with specific indications for use of the drugs. Finally, it is possible that the concordance between the DDD and days' supply method could be different in cohorts of 'prevalent' drug users, due to differences in starting doses versus those that may change in long-time users because of titration or other dose adjustment.

Conclusion

In conclusion, duration of exposure estimated using DDDs does not always correspond with duration of exposure estimated using days' supply. Our results elucidate certain drug classes for which DDDs fairly accurately correspond with days' supply. We have also identified certain classes for which investigators should consider adjusting estimated exposure durations for over- or under-estimation, although further work is required to find the best method of estimating exposure to intermittently used drugs. Additional work is needed to examine specific factors, such as age, geography, different indications for drugs and renal function that can affect the concordance between exposure duration estimated using DDDs and days' supply.

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Figure 1.

Median duration of exposure as measured by two methods: days' supply and Defined Daily Doses (DDD).

Legend: *ACE-inhibitors – angiotensin converting enzyme inhibitors, PPIs – proton pump inhibitors, ns-NSAIDs – non-selective non-steroidal anti-inflammatory drugs.

Figure 2.

Proportions of patients where both measurements agree, where DDD has overestimated days' supply and where DDD has underestimated days' supply.

Legend: *ACE-inhibitors – angiotensin converting enzyme inhibitors, PPIs – proton pump inhibitors, ns-NSAIDs – non-selective non-steroidal anti-inflammatory drugs.

Table 1

Baseline demographics of study subjects

	ACE-inhibitors*	Statins	Metformin	Atypical antipsychotics	PPIs*	Warfarin	Coxibs*	ns-NSAIDs*
No. of new users	808,529	929,137	473,666	1,234,506	1,954,845	143,885	827,899	3,205,841
Female - n (%)	498,897 (62%)	598,5836 (64%)	331,938 (70%)	667,596 (54%)	1,331,356 (68%)	91,410 (64%)	600,367 (73%)	2,358,711 (74%)
Mean age - years (sd)	46.1 (13.5)	48.3 (11.4)	43.7 (14.2)	28.1 (16.7)	36.4 (17.0)	46.3 (14.2)	42.4 (14.2)	32.5 (14.7)
Mean comorbidity score⁺ - (sd)	0.6 (1.6)	0.5 (1.4)	0.5 (1.3)	0.7 (1.1)	0.6 (1.4)	2.1 (2.5)	0.4 (1.2)	0.3 (0.8)
Race/ethnicity - n (%)								
White	339,755 (42%)	427,154 (46%)	196,650 (42%)	692,416 (56%)	996,806 (51%)	76,073 (53%)	390,955 (47%)	1,634,479 (51%)
Black	233,463 (29%)	197,741 (21%)	120,499 (25%)	299,644 (24%)	401,764 (21%)	39,245 (27%)	184,998 (22%)	823,513 (26%)
Hispanic	126,720 (16%)	157,685 (17%)	92,623 (20%)	120,053 (10%)	314,845 (16%)	12,826 (9%)	133,924 (16%)	459,047 (14%)
Asian	21,699 (3%)	38,391 (4%)	13,836 (3%)	12,201 (1%)	59,128 (3%)	1,974 (1%)	21,935 (3%)	76,697 (2%)
Other/unknown	86,892 (11%)	108,166 (12%)	50,058 (11%)	110,192 (9%)	182,302 (9%)	13,767 (10%)	96,087 (12%)	212,105 (7%)

* ACE-inhibitors – angiotensin converting enzyme inhibitors, PPIs – proton pump inhibitors, ns-NSAIDs – non-selective non-steroidal anti-inflammatory drugs.

⁺ Combined Charlson/Elixhauser Score²³

Table 2

Correlation coefficients for days' supply method with defined daily dose method.

	Correlation Coefficient
ACE-inhibitors	0.55 *
Statins	0.51 *
Metformin	0.34 *
Atypical antipsychotics	0.20 *
PPIs	0.81 *
Warfarin	0.58 *
Coxibs	0.79 *
ns- NSAIDs	0.80 *

ACE-inhibitors – angiotensin converting enzyme inhibitors, PPIs – proton pump inhibitors, ns- NSAIDs – non-selective non-steroidal anti-inflammatory drugs.

* denotes <0.0001