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Comparison of pharmacy database methods for determining prevalent chronic medication use

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Abstract

Background: Pharmacy dispensing data is frequently employed to identify prevalent medication use as a predictor or covariate in observational research studies. While several methods have been proposed for using pharmacy dispensing data to identify prevalent medication use, little is known about their comparative performance.

Objectives: We sought to compare the performance of different methods for identifying prevalent outpatient medication use.

Research Design: Outpatient pharmacy fill data was compared with medication reconciliation notes denoting prevalent outpatient medication use at the time of hospital admission for a random sample of 207 patients drawn from a national cohort of patients admitted to Veterans Affairs (VA) hospitals. Using reconciliation notes as the criterion standard, we determined the test characteristics of 12 pharmacy database algorithms for determining prevalent use of 11 classes of cardiovascular and diabetes medications.

Results: The best performing algorithms included a 180-day fixed look-back period approach (sensitivity 93%, specificity 97%, positive predictive value (PPV) 89%) and a medication-on-hand approach with a grace period of 60 days (sensitivity 91%, specificity 97%, PPV 91%). Algorithms that have been commonly used in previous studies, such as defining prevalent medications to include any medications filled in the prior year or only medications filled in the prior 30 days,

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performed less well. Algorithm performance was less accurate among patients recently receiving hospital or nursing facility care.

Conclusion: Pharmacy database algorithms that balance recentness of medication fills with grace periods performed better than more simplistic approaches, and should be considered for future studies which examine prevalent chronic medication use.

Keywords

Pharmaceutical Databases; Drug prescribing; Pharmacoepidemiology; Quality of care; Research Methodology

INTRODUCTION

The assessment of prevalent medication use is important for researchers seeking to study relationships between drug exposure and clinical outcomes. Many studies seeking to determine cross-sectional drug exposure have employed pharmacy dispensing or pharmacy claims data, including US commercial claims, Veterans Affairs (VA) pharmacy databases, Medicare Part D, Medicaid, as well as government databases in other countries. Studies of prescribing outcomes often require investigators to accurately determine which medications patients are taking at a particular point in time, for example to determine the association between medication exposure and subsequent clinical outcomes, to examine concurrent use of multiple medications, or to determine the relationship between a clinical event such as the receipt of a new test result or diagnosis and subsequent changes in prescribing.

There are few best practices for defining prevalent, also termed active or cross-sectional, medication exposure.[1] This evidence gap is in part due to a paucity of high-quality validation data both about the accuracy of individual approaches and about the comparative performance of different pharmacy database approaches in the same study population.[1–12] Common methods in the literature include fixed look-back period and medication-on-hand approaches. Fixed look-back period approaches define prevalent mediations as all medications filled in a specified date rage preceding the study index date, which may lead to misclassification of medications no longer in use. In contrast, medication-on-hand approaches define prevalent medications as those for which the most recent fill provided sufficient supply to last through the study index date, with or without a grace period, which may lead to undercounting medications for which patients do not have perfect adherence (Figure 1).

The majority of prior comparison studies have examined differing look-back period durations,[2–7] but few have directly compared fixed look-back period approaches against medication-on-hand approaches.[9–12] As a result, the tradeoffs of differing specifications for look-back periods, minimum number of fills, and grace periods remains poorly understood. Furthermore, prior research seeking to validate measures of prevalent medication use has largely relied on voluntary patient surveys to establish a comparison “gold standard”, an approach which risks two major biases.[1] First, due to participation bias, participants in surveys may significantly differ from the underlying population. Second, voluntary reporting

may be inaccurate due to forgetfulness as well as both over- and under-reporting of medication use due to social desirability bias.

To address these gaps, we conducted a retrospective cohort study of older adults who were hospitalized in the VA Health Administration, the largest integrated health system in the US. During hospitalization, high quality lists of medications in use at the time of hospital admission are frequently established by clinicians as part of routine clinical care, providing an ideal criterion standard to compare pharmacy database algorithms against. Using the national VA outpatient pharmacy database, we developed twelve pharmacy database algorithms for identifying prevalent medication use and compared them against this criterion standard measure to determine the accuracy of each approach. Lastly, we examined how algorithm accuracy varied when including patients who were likely to receive medications from sources other than VA outpatient pharmacy, including medication fills from inpatient, skilled nursing facility, and non-VA outpatient pharmacies.

METHODS

Study population

The study population was randomly sampled from a larger retrospective cohort study of older adults hospitalized in the VA.[13] The VA Health Administration provides care for 9 million enrolled Veterans through an integrated system of over 1,000 outpatient clinics and 170 hospitals which use a national pharmacy benefit management system. The original study cohort included all older adults with hypertension and/or diabetes who received regular outpatient care in the VA (≥80% of outpatient visits) and who were admitted to a VA hospital for common medical conditions. To develop a criterion standard for prevalent medication use, a random sample of patients from the larger study cohort was selected for detailed chart review to determine outpatient mediation use on the day of admission.

Study medications

In the VA, all prescribed medications are filled in VA pharmacies which maintain a common national formulary and national dispensing database (VA Pharmacy Benefits Management database). Patients are strongly incentivized to obtain their medicines through VA pharmacies, including those which might be recommended by any non-VA providers, due to tiered co-payment system that often provides medication at much lower costs than external pharmacies. Chronic medications are typically filled in increments of 30, 60, or 90 days.

For each patient, prevalent medication use was determined using two sources, chart review of VA electronic health records and the national VA pharmacy database. Eleven chronic medication classes were examined, seven cardiovascular medication classes (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, anti-anginals, beta-blockers, calcium channel blockers, non-loop diuretics, and other antihypertensives) and four diabetes medication classes (insulins, biguanides, sulfonylureas, and other hypoglycemic agents).

Individual medications were grouped into classes by VA National Drug Formulary drug class code to accommodate intra-class substitutions, as clinicians or pharmacists may substitute medications within the same class due to formulary changes or dosing frequency

preferences. (Appendix 1). Combination medications were split into their component ingredients.

Chart review of medication use

During hospitalization, many patients will be seen by a physician or pharmacist to conduct a formal medication reconciliation, reviewing and confirming which outpatient medications were actively being used by the patient prior to hospitalization with the goal of preventing prescribing errors.[13] This detailed review process extends beyond the routine listing of previously prescribed medications copied from the electronic health record. Medication reconciliation consists of a thorough review of medications listed in the electronic health record, medications received from other sources including over the counter medications, discussion with patient and caretakers on current use patterns, and clarification of any discrepancies between patient report and prior documentation.

The availability of health professionals to conduct medication reconciliations may vary by time of day, day of week, and hospital. Thus, as not all patients may receive a medication reconciliation during hospitalization, two authors (SN and EX) reviewed charts for each patient during the dates of hospitalization to determine the presence of a non-automated list of admission medications. A non-automated list was defined as either a pharmacist medication reconciliation note or a discharge summary note containing both a list of discharge medications and a list of changes to admission medications that were made during hospitalization. For charts with non-automated medication lists, two authors (TSA and CMW) identified whether the patient was listed as actively using each study medication class on the day of hospital admission (index date).

Pharmacy database measures

For each patient, we obtained VA pharmacy dispensing data including drug name, dose, date of fill, days supply of medication, and quantity supplied, to create a supply-diary of medication fills for the one-year preceding the index hospitalization for each medication class. All drugs dispensed within a therapeutic class were counted as interchangeable.

We next constructed a set of twelve algorithms for measuring prevalent medication use, listed in Table 1, based on previously used approaches in the literature and a published framework for determining medication counts.[15] Pharmacy database algorithms included six fixed look-back period approaches, requiring a minimum number of fills for the medication class within a specified look-back duration, with each algorithm varying requirements for look-back duration and number of fills. Additionally, six medication-on-hand approaches were examined, defining prevalent medications as those for which the most recent refill date provided sufficient supply to last through the study index date plus a variable grace period. Grace periods were included to account for carryforward of previously stockpiled medications and transient non-adherence.

External pharmacies

We then sought to determine whether patients were exposed to medication sources outside of the outpatient VA pharmacy. Our study population included patients who received ≥ 80%

of their outpatient care from the VA, and thus were expected to regularly receive medications from the VA pharmacy, however these patients may have received medications from outside pharmacies. Thus, using chart review, we identified whether patients had documentation of receiving any study medication classes from a non-VA pharmacy source. As patients who are hospitalized or residing in nursing facilities may receive medications from inpatient rather than outpatient pharmacies, we used VA and Medicare claims to identify patients who had been discharged from a hospital and/or were residing in a nursing facility in the 30 days preceding the index date.

Statistical analysis

Our primary analyses were restricted to patients without evidence of receiving medications from non-VA sources and who did not receive hospital or nursing facility care in the 30 days prior to the index date. We first calculated the test characteristics of each pharmacy database algorithm for identifying prevalent medication classes for each patient, compared to the criterion standard chart review medication reconciliation. We report the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and receiver operating characteristic (ROC) area. **All test characteristics were calculated using the *diagt* command in Stata. The sensitivity is the probability that a medication class identified as in active use by hospitalization medication list (criterion standard) was also identified by the pharmacy database algorithm. The specificity is the probability that a medication class identified as not in active use by the hospitalization medication list was also identified as not in active use by the pharmacy database algorithm. As each algorithm provided a dichotomous result (identified medication as in use or not in use) the ROC area is calculated by the *diagt* command as the average of the sensitivity and specificity to provide one overall measure of test performance.** The PPV is the probability a drug identified by the pharmacy database algorithm was also recorded on the hospitalization medication list.

In secondary analyses, we examined the test characteristics of the best performing fixed look-back period and medication-on-hand algorithms for each of the 11 medication classes individually. The best performing algorithms were selected based on highest ROC area. We then calculated test characteristics for the same two algorithms, while varying patient inclusion criteria to include all patients, patients with and without evidence of non-VA medication use, and patients with and without hospitalization or nursing facility stay in the prior 30 days.

We determined statistical significance using 95% confidence intervals. All analyses were conducted using Stata (version 14.1, College Station, TX). This research was approved by the institutional review boards of the San Francisco Veteran Affairs Medical Center and the University of California, San Francisco.

RESULTS

Of 598 patient charts screened, 207 charts (35%) had non-automated medication lists compiled by physicians or pharmacists. The mean age was 76 (SD 8.2) and the majority of patients were male (96%) and white (78%). Nearly half of patients were admitted with

pneumonia (103, 50%), with the remainder admitted with urinary tract infections (86, 41%) or venous thromboembolism (16, 9%).

Of the 207 patients included in the study, eight were listed as receiving non-VA medications in the chart review, six were residing in a skilled nursing facility prior to hospitalization, and 22 were hospitalized in 30 days preceding the index date. The primary analyses were limited to the 174 patients without evidence of receiving medications from a non-VA pharmacy and without hospital discharge or skilled nursing facility stay in preceding 30 days.

Table 2 describes the overall test characteristics for each pharmacy database algorithm. The majority of algorithms had high accuracy compared to chart review, with nine of twelve having an ROC area greater than 0.90. All approaches had a specificity greater than 90%, while sensitivity was more variable.

For fixed look-back periods, sensitivity improved with longer look-back durations, ranging from 36% for algorithm A, the fixed look-back period approach with the shortest look-back duration of 30 days, to 95% for algorithm D, the fixed look-back period approach with the longest look-back duration of 365 days. Increasing look-back duration length also led to declining specificity and PPV. Adding a requirement for at least two prescriptions (algorithms E and F) slightly improved the specificity but substantially decreased the sensitivity compared to requiring only one prescription. For medication-on-hand approaches, grace periods with longer durations resulted in improved sensitivity but poorer specificity and PPV.

Algorithms C (fixed look-back approach with 180-day look-back period) and I (medication-on-hand approach with 60-day grace period) were identified as the best performing methods as both had ROC areas of 0.95 and high PPVs, and were chosen for additional analyses that explored the accuracy of these methods under different circumstances. Figure 2, depicts the test characteristics for both algorithms, by drug class. Due to a low prevalence, estimates for ARBs, antianginals, other antihypertensives, and other hypoglycemics were limited by wide confidence intervals. Algorithm performance was similar across each of the remaining drug classes, with generally similar point estimates and overlapping confidence intervals across drugs for each type of test characteristic. For algorithm C sensitivity ranged from 86% to 97% and specificity ranged from 86% to 99%. For algorithm I sensitivity ranged from 86% to 96% and specificity ranged from 89% to 100%.

Table 3 examines the performance of algorithms C and I when varying study population inclusion and exclusion criteria. When no exclusion criteria were applied to the cohort, the sensitivity of both measures dropped slightly (93% to 91% for algorithm C and 91% to 89% for algorithm I) while the specificity remained similar to the primary analytic cohort. In subgroup analyses, the accuracy of both algorithms was substantially poorer for patients who had chart review evidence of receiving non-VA medications and for patients receiving hospital or skilled nursing facility in the previous 30 days.

DISCUSSION

Our analyses demonstrate that the VA pharmacy database, when properly specified, identified prevalent chronic medication use with high accuracy compared to a criterion standard of medication reconciliation notes. Both fixed look-back period approaches and medication-on-hand approaches performed well when algorithms balancing requirements for recentness of medication fills with flexibility for imperfect adherence were chosen. More simplistic approaches, which classified prevalent use by only very recent fills, had high rates of false negative misclassification, likely due to prior stockpiling and imperfect adherence. High-performing approaches were robust across multiple chronic medication classes but performed less well when patients with high likelihood for receiving medications from outside sources were included in the study sample. These results provide a best practice standard for future studies seeking to measure prevalent use of chronic medications.

Our findings build on prior studies seeking to validate pharmacy database algorithms in three important ways. First, our criterion standard, hospital medication reconciliation notes, was chosen to capitalize on a detailed source of medication use information which was obtained as a routine part of clinical care. This approach largely overcomes the response and recall biases which limit many prior studies that have relied on patient self-report through voluntary surveys and interview. The use of two-stage chart review also avoided the inclusion of lower-quality automated medication lists extracted from medication ordering systems. Nonetheless, even medication reconciliation encounters by clinicians may not be a perfect “gold standard” for medication exposure, as prompted recall informed by an existing medication list may still be subject to recall bias and patient adherence may be variable.

Second, prior studies have rarely compared multiple pharmacy database approaches within the same study population. **Prior studies have reported sensitivity of fixed look-back period and medication-on-hands to range from 35% to 97% but have examined a wide variety of different pharmacy databases, patient populations, and criterion standards and thus are not directly comparable.**[1] Our analyses, comparing six fixed look-back period approaches and six medication-on-hand approaches, allows for a more detailed understanding of the tradeoffs in sensitivity and specificity when specifying pharmacy database algorithms to identify prevalent medication use. A central finding of this study is that algorithms which include grace periods or longer look-back periods to account for imperfect adherence and refill patterns had improved sensitivity with minimal decreases in specificity, compared with algorithms with narrow exposure windows.

Third, our study is the first to our knowledge, to validate approaches to determining prevalent medication use within the VA Health Administration. The VA is a major source of pharmacoepidemiology research due to its national pharmacy database. As the VA operates as an integrated health system, our findings are likely generalizable to other integrated health systems which operate their own pharmacies, as well as government-sponsored health systems with pharmacy benefits. Nonetheless, additional high-quality validation studies of approaches for identifying prevalent medication use should be conducted in other pharmacy databases commonly used for pharmacoepidemiology research. **Importantly, the VA serves a primarily male patient population, though the medications included in this study are**

frequently used by both male and female patients, however generalizability of these findings to chronic medications used primarily by women (e.g. oral contraceptives) is limited.

Although the overall accuracy of pharmacy database algorithms for determining prevalent medication use was high, we found that patient characteristics may have a substantial influence on algorithm performance. Even in the VA, where patients are incentivized to fill their prescriptions in the internal pharmacy, patients may receive medications from outside sources. Patients recently receiving care from facilities with independent pharmacies such as nursing facilities and hospitals may receive a supply of medications to be taken at home upon discharge.[16] This supply if not captured may impact adherences estimates[17] and we found that the sensitivity of pharmacy database approaches for estimating prevalent medication use are significantly lower in this population. This fragmentation of care is a common obstacle in pharmacoepidemiology research, particularly in the US, and addressing it requires careful attention to participant inclusion and exclusion criteria during study design. **Additionally, patients receiving VA benefits have the option to seek care from physicians outside of the VA and may obtain some of all of their care and medications from external sources, most notably Medicare Part D.**[18] In this study, we limited our study population to patients who received at least 80% of their outpatient care from the VA based upon administrative claims, however using detailed chart review we determined an additional 4% of our study population received medications from non-VA sources. Future studies utilizing pharmacy databases should clearly describe how the possibility of external medication use is addressed in the study design, to avoid underestimation of prevalent medication use.

Medication class is another key consideration in selecting a pharmacy database approach. The best performing algorithms in this study performed similarly across all studied classes, however we examined only chronic cardiovascular and diabetes medications. The performance of study algorithms is likely to be similar for other classes used on a chronic daily basis (e.g. antidepressants, anticoagulants, antiepileptics, lipid-lowering medications, thyroid medications, and daily analgesics). However, we did not examine medications more often used for limited durations (e.g. antibiotics or steroids) or medication used episodically (e.g. as-needed analgesics). These medications pose unique challenges in measuring prevalent medication use[19] and are likely to require algorithms calibrated to a shorter look-back period. Thus the performance of the described study algorithms should not be extrapolated to these classes, and studies examining prevalent use of intermittent or short duration medications require further validation. Furthermore, medications routinely available over-the-counter and without a prescription may not be captured by pharmacy claims or dispensing databases[20–21] Similarly, medications purchased without the use of a pharmacy benefit (e.g. with cash or drug coupons) may be captured by dispensing databases but not pharmacy claims leading to underestimation of prevalent use, regardless of algorithm specification.[22–24]

In conclusion, pharmacy databases can be used to measure prevalent chronic medication use with high accuracy compared to a criterion standard of hospital medication reconciliations. Both fixed look-back period and medication-on-hand algorithms performed well when

algorithms that balanced recentness of medication fills with grace periods to account for imperfect adherence were specified. Future studies examining prevalent medication use should carefully consider both medication class and patient characteristics when selecting a study population and pharmacy database approach.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Anderson TS, Xu E, Whitaker E, et al. A systematic review of methods for determining cross-sectional active medications using pharmacy databases. Pharmacoepidemiol Drug Saf. 2019; 28(4): 403–421. [PubMed: 30761662]
2. Pit SW, Byles JE, Cockburn J. Accuracy of telephone self-report of drug use in older people and agreement with pharmaceutical claims data. Drugs Aging. 2008;25(1):71–80. [PubMed: 18184031]
3. Rikala M, Hartikainen S, Sulkava R, et al. Validity of the Finnish Prescription Register for measuring psychotropic drug exposures among elderly finns: a population-based intervention study. Drugs Aging. 2010;27(4):337–49. [PubMed: 20359263]
4. Allin S, Bayoumi AM, Law MR, et al. Comparability of self-reported medication use and pharmacy claims data. Health Rep. 2013;24(1):3–9.
5. Hafferty JD, Campbell AI, Navrady LB, et al. Self-reported medication use validated through record linkage to national prescribing data. J Clin Epidemiol. 2018;94:132–142. [PubMed: 29097340]
6. Brown DW, Anda RF, Felitti VJ. Self-reported information and pharmacy claims were comparable for lipid-lowering medication exposure. J Clin Epidemiol. 2007;60(5):525–9. [PubMed: 17419964]
7. Fujita M, Sato Y, Nagashima K, et al. Validity assessment of self-reported medication use by comparing to pharmacy insurance claims. BMJ Open. 2015;5(11):e009490.
8. Lund BC, Chrischilles EA, Carter BL, et al. Development of a computer algorithm for defining an active drug list using an automated pharmacy database. J Clin Epidemiol. 2003;56(8):802–6. [PubMed: 12954474]
9. Lau HS, de Boer A, Beuning KS, et al. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol. 1997;50(5):619–25. [PubMed: 9180655]
10. Sjahid SI, van der Linden PD, Stricker BH. Agreement between the pharmacy medication history and patient interview for cardiovascular drugs: the Rotterdam elderly study. Br J Clin Pharmacol. 1998;45(6):591–5. [PubMed: 9663815]
11. Klungel OH, de Boer A, Paes AH, et al. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in The Netherlands. Pharm World Sci. 1999;21(5):217–20. [PubMed: 10550846]
12. Nielsen MW, Søndergaard B, Kjøller M, et al. Agreement between self-reported data on medicine use and prescription records vary according to method of analysis and therapeutic group. J Clin Epidemiol. 2008;61(9):919–24. [PubMed: 18468858]
13. Anderson TS, Wray C, Jing B, et al. Intensification of Older Adults' Blood Pressure Medications at Hospital Discharge. BMJ. 2018;362:k3503. [PubMed: 30209052]

14. Mueller SK, Sponsler KC, Kripalani S, et al. Hospital-based medication reconciliation practices: a systematic review. Arch Intern Med. 2012;172(14):1057–69. [PubMed: 22733210]
15. Goedken AM, Lund BC, Cook EA, et al. Application of a framework for determining number of drugs. BMC Res Notes 2016; 9:272. [PubMed: 27178197]
16. Sattler EL, Lee JS, Perri M. Medication (re)fill adherence measures derived from pharmacy claims data in older Americans: a review of the literature. Drugs Aging. 2013;30(6):383–99. [PubMed: 23553512]
17. Dong YH, Choudhry NK, Krumme A, et al. Impact of hospitalization on medication adherence estimation in claims data. J Clin Pharm Ther. 2017;42(3):318–328. [PubMed: 28370404]
18. Stroupe KT, Smith BM, Bailey L, et al. Medication acquisition by veterans dually eligible for Veterans Affairs and Medicare Part D pharmacy benefits. Am J Health Syst Pharm. 2017;74(3): 140–150. [PubMed: 28122756]
19. Cohen JM, Wood ME, Hernandez-Diaz S, et al. Agreement between paternal self-reported medication use and records from a national prescription database. Pharmacoepidemiol Drug Saf. 2018;27(4):413–421. [PubMed: 29488294]
20. Delaney JA, Biggs ML, Kronmal RA, et al. Demographic, medical, and behavioral characteristics associated with over the counter non-steroidal anti-inflammatory drug use in a population-based cohort: results from the Multi-Ethnic Study of Atherosclerosis. Pharmacoepidemiol Drug Saf. 2011;20(1):83–9. [PubMed: 21182156]
21. Qato DM, Alexander GC, Conti RM, et al. Use of Prescription and Over-the-counter Medications and Dietary Supplements Among Older Adults in the United States JAMA. 2008; 300(24): 2867–2878. [PubMed: 19109115]
22. Lauffenburger JC, Balasubramanian A, Farley JF, et al. Completeness of prescription information in US commercial claims databases. Pharmacoepidemiol Drug Saf. 2013;22(8):899–906. [PubMed: 23696101]
23. Gisev N, Pearson SA, Karanges EA, et al. To what extent do data from pharmaceutical claims under-estimate opioid analgesic utilisation in Australia? Pharmacoepidemiol Drug Saf. 2018;27(5):550–555. [PubMed: 29047196]
24. Cepeda MS, Fife D, Denarié M, et al. Quantification of missing prescriptions in commercial claims databases: results of a cohort study. Pharmacoepidemiol Drug Saf. 2017;26(4):386–392. [PubMed: 28120552]

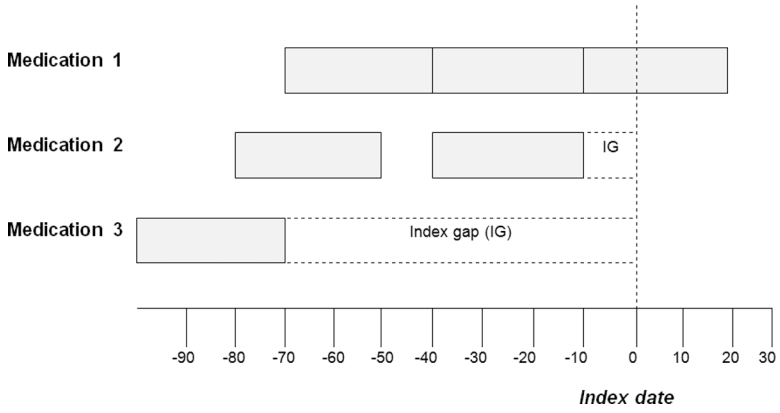

Figure 1:

Approaches for determining prevalent medication use

In the figure, solid bars represent days supplied by medication fills for three medications prescribed to a hypothetical patient. The index gap (IG) is the period between the last day supplied by the most recent fill and the index date. Medication 1 has an index gap of 0 days, medication 2 has an index gap of 10 days, and medication 3 has an index gap of 70 days.

The two primary study approaches are described:

Fixed look-back period approaches (Algorithms A-F): Defines prevalent medications as those for which a fill occurred during a specified period prior to the index date, regardless of the index gap. Algorithms A-F vary the look-back duration from 30 days to 365 days and the number of fills required to occur prior to the index date. Using a fixed look-back period of 30 days (algorithm A) would classify only medication 1 as prevalent, while using a fixed look-back period of 90 days (algorithm B) would classify medications 1 and 2 as prevalent.

Medication-on-hand approach (Algorithms G-L): Classifies medications based on the index gap, defining prevalent medications those for which the most recent refill date provided sufficient supply to last through the study index date with or without a grace period (i.e., an allowable index gap). Using a medication-on-hand approach without a grace period (algorithm G) only medication 1 would be classified as prevalent, while using a medication-on-hand approach with a fixed 90-day grace period (algorithm J) would classify all three medications as prevalent. Using a medication-on-hand approach with a variable grace period for 10% of the prior fill days supplied (algorithm K), would allow a 3-day grace period (10% of 30 days supplied) and would classify only medication 1 as prevalent.

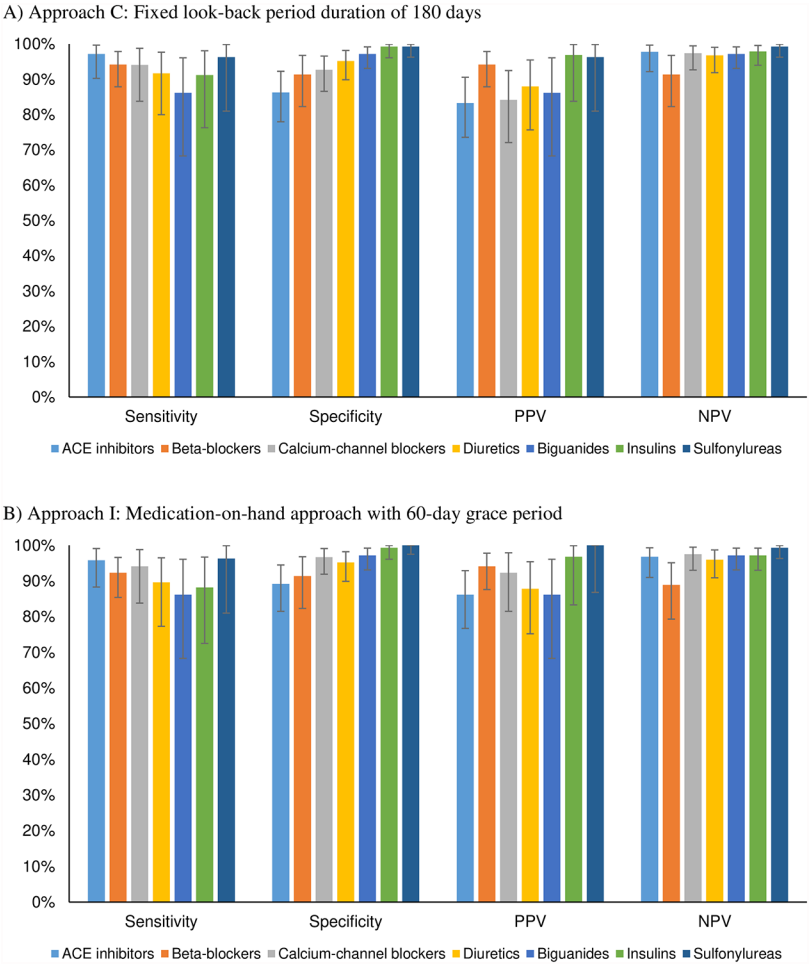

Figure 2.

A-B: Performance of fixed look-back period and medication-on-hand approaches, by drug class

Note: ACE inhibitors, angiotensin-converting enzyme inhibitors. Results for angiotensin II receptor blockers, anti-anginals, other anti-hypertensives and other hypoglycemics not displayed due to population prevalence less than 10% and thus unstable point estimates with very wide confidence intervals

Table 1:

Pharmacy database approaches for determining prevalent medication use

Approach	Requirements for prevalent medication use
Fixed-look back period approaches	
A	One fill required in the 30 days prior to index date
B	One fill required in the 90 days prior to index date
C	One fill required in the 180 days prior to index date
D	One fill required in the 365 days (1 year) prior to index date
E	Two fills required in the 180 days prior to index date
F	Two fills required in the 365 days (1 year) prior to index date
Medication-on-hand approaches	
G	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply]
H	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply **+ a 30-day grace period**]
I	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply **+ a 60-day grace period**]
J	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply **+ a 90-day grace period**]
K	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + (**110% of the days supply**)]
L	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + (**125% of the days supply**)]

Table 2:

Comparison of pharmacy database algorithms

	Requirements for prevalent medication use	Sensitivity	Specificity	PPV	NPV	ROC Area
Fixed look-back period approaches						
A	One fill of ≥ 25 days supply required in prior 30 days	36 (32 to 41)	99 (99 to 99)	96 (91 to 98)	85 (83 to 87)	0.68 (0.66 to 0.71)
B	One fill of ≥ 25 days supply required in prior 90 days	81 (77 to 85)	98 (97 to 98)	92 (89 to 95)	95 (94 to 96)	0.90 (0.88 to 0.92)
C	One fill of ≥ 25 days supply required in prior 180 days	93 (90 to 95)	97 (96 to 97)	89 (86 to 92)	98 (97 to 98)	0.95 (0.94 to 0.96)
D	One fill of ≥ 25 days supply required in prior 365 days (1 year)	95 (93 to 97)	93 (92 to 94)	80 (76 to 84)	98 (98 to 99)	0.95 (0.94 to 0.96)
E	Two fills of ≥ 25 days supply required in prior 180 days	74 (69 to 78)	98 (97 to 98)	91 (87 to 94)	93 (92 to 94)	0.86 (0.84 to 0.88)
F	Two fills of ≥ 25 days supply required in prior 365 days (1 year)	89 (86 to 92)	95 (94 to 96)	85 (81 to 88)	97 (96 to 98)	0.93 (0.91 to 0.94)
Medication-on-hand approaches						
G	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply]	77 (73 to 81)	98 (97 to 99)	93 (90 to 96)	94 (93 to 95)	0.88 (0.86 to 0.90)
H	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply **+ 30 days**]	87 (83 to 90)	98 (97 to 98)	92 (89 to 95)	96 (95 to 97)	0.93 (0.91 to 0.94)
I	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply **+ 60 days**]	91 (88 to 94)	97 (96 to 98)	91 (88 to 94)	97 (96 to 98)	0.95 (0.93 to 0.96)
J	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + days supply **+ 90 days**]	92 (89 to 95)	97 (96 to 97)	89 (86 to 92)	98 (97 to 98)	0.95 (0.94 to 0.96)
K	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + (**110% of the days supply**)]	80 (76 to 84)	98 (97 to 99)	93 (90 to 95)	95 (93 to 96)	0.90 (0.88 to 0.92)
L	Index date falls within the period from the most recent preceding fill date for a drug through the [fill date + (**125% of the days supply**)]	85 (81 to 88)	98 (97 to 98)	93 (89 to 95)	96 (94 to 97)	0.92 (0.90 to 0.93)

Note: Analysis includes 174 patients and 11 medication classes (total of 1914 patient/medication class comparisons): angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, antianginals, beta-blockers, calcium-channel blockers, diuretics, other antihypertensives, insulins, biguanides, sulfonylureas, and other hypoglycemics.

Table 3:

Performance of fixed look-back period and medication-on-hand approaches with varying patient inclusion criteria

	Approach C: Fixed look-back period duration of 180 days				Approach I: Medication-on-hand with 60-day grace period			
	Sensitivity	**Specificity**	**PPV**	**NPV**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
All patients (N=207)	91 (88 to 93)	96 (95 to 97)	86 (83 to 89)	98 (97 to 98)	89 (86 to 92)	97 (96 to 98)	89 (86 to 92)	97 (96 to 98)
Patients with evidence of receiving medications from a non-VA pharmacy (N=8)*	53 (27 to 77)	94 (86 to 98)	69 (39 to 91)	89 (80 to 95)	53 (28 to 77)	94 (86 to 98)	69 (39 to 91)	89 (80 to 95)
Patients with hospital discharge or skilled nursing facility stay in preceding 30 days (N=28)*	77 (63 to 88)	93 (89 to 96)	68 (54 to 79)	95 (92 to 98)	73 (59 to 84)	95 (91 to 97)	73 (59 to 84)	95 (91 to 97)
Primary analysis: Patients without evidence of receiving medications from a non-VA pharmacy and without hospital discharge or skilled nursing facility stay in preceding 30 days (N=174)	93 (90 to 95)	97 (96 to 97)	89 (86 to 92)	98 (97 to 98)	91 (88 to 94)	97 (96 to 98)	91 (88 to 94)	97 (96 to 98)

*Three patients had both evidence of receiving medications from a non-VA pharmacy and hospital discharge or skilled nursing facility stay in preceding 30 days.