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A systematic review of methods for determining cross-sectional active medications using pharmacy databases

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Abstract

Purpose: Pharmacy dispensing databases are often used to identify patients' medications at a particular time point, for example to measure prescribing quality or the impact of medication use on clinical outcomes. We performed a systematic review of studies that examined methods to assess medications in use at a specific point in time.

Methods: Comprehensive literature search to identify studies that compared active medications identified using pharmacy databases to medications identified using non-automated data sources. Two investigators independently reviewed abstracts and full-text material.

Results: Of 496 studies screened, 29 studies evaluating 50 comparisons met inclusion criteria. Twenty-nine comparisons evaluated fixed look-back period approaches, defining active medications as those filled in a specified period prior to the index date (range 84-730 days). Fourteen comparisons evaluated medication-on-hand approaches, defining active medications as

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AUTHOR CONTRIBUTIONS

Dr. Anderson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Anderson and Steinman.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: Anderson.

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: Anderson.

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Study supervisor: Steinman.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

DISCLAIMER

The views expressed herein are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs or the University of California, San Francisco.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

those for which the most recent fill provided sufficient supply to last through the study index date. Sensitivity ranged from 48% to 93% for fixed look-back period approaches and 35% to 97% for medication-on-hand approaches. Interpretation of comparative performance of methods was limited by use of different reference sources, target medication classes, and databases across studies. In four studies with head-to-head comparisons of these methods, sensitivity of the medication-on-hand approach was a median of 7% lower than the corresponding fixed look-back approach.

Conclusions: The reported accuracy of methods for identifying active medications using pharmacy databases differs greatly across studies. More direct comparisons of common approaches are needed to establish the accuracy of methods within and across populations, medication classes, and databases.

Keywords

databases; drug prescribing; pharmaceutical; Pharmacoepidemiology; quality of care; research methodology; systematic review

1 | INTRODUCTION

Automated pharmacy dispensing and claims databases are commonly used to measure medication exposure. Despite well-described limitations, pharmacy dispensing data are convenient, objective, and allow the study of large populations for which other methods of assessing medication exposure may be infeasible.¹ Increasingly researchers and health systems have focused on examining prescribing quality and clinical outcomes, which includes topics of polypharmacy, duplication of therapy, medication interactions, adherence to prescribing guidelines, and changes in medication use after clinical events. These types of research questions frequently require that investigators establish a list of medications being taken by a patient at a fixed point in time, also referred to as an active medication list or cross-sectional medication list.^{2,3}

In contrast to studies focused on adherence, where standard measures have been established and compared,⁴⁻⁷ there are no consensus measures for establishing active medication lists, and in many studies, approaches used to identify active medications are incompletely described.⁸ Adherence studies generally examine longitudinal medication use, and cohort entry is often defined as the first fill of the study medication being examined, ie, new user cohort study designs. However, these approaches are not suited to evaluating cross-sectional medication use, as cohort entry may be defined by a clinical event, such as occurrence of a potentially medication related adverse event, hospitalization, test result, or new diagnosis. Furthermore, case-control studies examining the association between a clinical event (eg, falls, acute coronary syndrome, infection) and prior drug exposure require careful attention to defining medication exposure at the time of the clinical outcome of interest.

In the absence of consensus measures, researchers have employed a variety of definitions of active medication use. Two broad approaches are commonly used. The fixed look-back period approach examines all medication filled within a set period prior to the study index date. The medication-on-hand approach (also termed legend duration approach) classifies

medications for which the most recent fill provided sufficient supply to last through the study index date as active. However, there is a paucity of literature methodically examining and comparing these common approaches for establishing active medication lists. The lack of a comprehensive assessment of validated measures is a major impediment to identifying best practices and for defining what future work is needed to improve the accuracy of measurement of active medication use in both pharmacoepidemiology research and quality improvement initiatives. In the study, we systematically review the literature to identify studies which evaluated the accuracy of pharmacy database methods for establishing active medication lists.

2 | METHODS

2.1 | Search strategy

We conducted a search of English language literature using PubMed, Embase, and Google Scholar to identify studies that evaluated active medication use using pharmacy databases which were published between January 1 1990 and October 1 2017. The search strategy was developed in PubMed using Medical Subject Headings (MeSH) search terms and translated into searches tailored to Embase and GoogleScholar with the assistance of a research librarian (EW). Complete search strings for each database listed in Appendix 1. We additionally searched the reference list for each article which met study inclusion criteria to identify additional articles of possible interest.

2.2 | Identification and selection of articles

Two study investigators (TA and EX) independently reviewed study abstracts to identify potentially relevant articles for retrieval using Covidence. The study protocol was registered on PROSPERO (CRD42018085584) in February 2018.

For title and abstract screening, we examined all original research publications which used pharmacy databases to establish a patient-level list of medications being used at a fixed point in time, regardless of the characteristics of the study population, sample size, setting, or type of pharmacy database. We included studies which established a comprehensive list of medications used by a patient and those which established a focused list medication classes (ie, cardiac medications). Studies which examined medication use over a period of time (period prevalence) rather than at a fixed point were not included (ie, studies of medication use during pregnancy).

Two study investigators (TA and EX) independently reviewed the full-text articles, applying the above exclusion criteria. For studies meeting the initial criteria, we then determined whether the pharmacy database approaches used to identify active medications were compared with an alternative approach (ie, patient self-report or medical records) and included only studies with validation components. Disagreements between reviewers were resolved by consensus with the input of a third investigator (MAS). See PRISMA flow diagram for final study population (Figure 1).

2.3 | Data analysis

First, we extracted study characteristics including primary aim, country, pharmacy database examined, clinical setting, study population, sample size, year, and alternative approach against which pharmacy databases were compared.

Second, we identified the criteria for classifying a medication as active, based upon a published framework for determining the number of drugs used by a patient.⁸ Extracted elements included the scope of medications examined, consideration of prior fill history (medication fills which occurred prior to the most recent fill in determining if a medication was active), allowable index gap (the length of time before the index date in which a medication must be filled to be counted as active), consideration of postindex fills (fills which occurred after the index date), and any other factors used to determine active medications.

Third, we extracted the results of the pharmacy database comparison. For each study, we extracted the number of medications identified as active by the pharmacy database approach and the comparator approach. This data was used to construct 2×2 tables from which we calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of pharmacy records compared with alternative methods. Though some studies referred to the pharmacy database as the gold standard, we converted all reported test characteristics such that the pharmacy database is the test metric compared with the alternative “gold-standard” approach. While establishing a true gold standard for drug exposure is challenging, calculating sensitivity and specificity provides important detail on the direction of misclassification between methods, and thus were our primary analysis. We secondarily calculated Cohen kappa statistic⁹ and the prevalence-adjusted and bias-adjusted kappa (PABAK)¹⁰ to assess concordance across studies. For studies which did not report the raw data necessary to construct a complete 2×2 table, we extracted the published test characteristics. For studies which reported test characteristics separately for individual drug classes, raw data for each class were summed when available; if not available, the median and range of test characteristics across drug classes were reported.

Lastly, we conducted a qualitative evaluation of the strengths and limitations of each pharmacy database method for establishing active medication lists.

3 | RESULTS

We identified 30 studies from eight countries which validated methods for establishing active medication lists using pharmacy databases against medication use data obtained from other sources (Table 1).¹¹⁻⁴⁰ Studies had variable patient inclusion criteria, often requiring evidence of medication claims in the database prior to the study period. The majority of studies (90%) involved patients recruited for a cohort study or interventional trial. Participation rates ranged from 38% to 86% but were often unreported. Eleven studies evaluated national government databases, five evaluated regional government databases, seven evaluated health system databases, and seven evaluated outpatient pharmacy databases. Fourteen studies compared pharmacy database approaches with patient interview,

seven to patient survey, four to chart review, one to pharmacist review of prescribing records, one to serum drug levels, and two to a combination of sources.

3.1 | Pharmacy database methods used to define an active medication

Eighteen studies evaluated a single approach for establishing an active medication list, and 12 compared multiple approaches yielding 51 total comparisons (Table 2). The scope of medications examined ranged from a single drug class to all prescribed medications. Twenty-nine comparisons in 20 studies used a fixed look-back period approach, classifying all medication filled by a patient in a specified time period (range 84-730 days) prior to the study index date as active. Only one study required more than one fill to classify a medication as active.³⁶ No studies required fills to have a minimum number of days supplied. For illustration, Figure 2 depicts hypothetical classifications of medications using different timeframes for both fixed look-back period and medication-on-hand approaches.

Fourteen comparisons in 11 studies used a medication-on-hand approach. Of these, seven comparisons had an allowable index gap of zero (no grace period), six included a grace period or fixed allowable index gap (range 3-60 days), and one included a flexible allowable index gap (requiring a gap of less than 60 days between the preindex fill and first postindex fill).³⁸ Only one comparison required multiple fills prior to the index date to be counted as active.²¹ Two studies included additional criteria for medications typically used short term or as needed.^{20,22}

Seven comparisons in three studies used an alternative method to define active medications. Six comparisons defined active medications as those filled within a fixed period which included both preindex fills and postindex fills.^{24,38} One study used a mathematical modeling approach to calculate personalized drug use periods for each patient based upon individual drug refill patterns.⁴⁰

3.2 | Performance of pharmacy database methods

The test characteristics of each pharmacy database method compared with other sources of active medication lists are listed in Table 3. Assessment of measure performance across studies was limited due to the use of different inclusion criteria, study populations, and comparator metrics. Comparisons examining fixed look-back period approaches reported variable sensitivity (48%-93% with majority between 70% and 85%) but high specificity (82%-100%, with majority greater than 90%). Among comparisons reporting results stratified by medication class, the sensitivity ranged from 29% to 100% with medications taken as needed and medications taken for short duration (eg, antibiotics and analgesics) having lower reported sensitivity than chronic medications. Similarly, the reported sensitivity of medication-on-hand approaches ranged from 35% to 96% (majority between 75% and 90%), while the reported specificity was generally higher (89%-100%).

3.3 | Comparisons of pharmacy database methods within studies

Eleven studies compared multiple pharmacy database approaches within the same study population. Four studies compared different look-back period durations,^{13,29,33,34} consistently demonstrating that longer durations resulted in higher sensitivity but lower

specificity and PPV. Two studies which also included postindex fills also demonstrated that increasing the overall duration examined resulted in higher sensitivity.^{24,37}

Four studies compared a fixed look-back period approach to a medication-on-hand approach.^{13-15,28} In these four studies, the sensitivity of the medication-on-hand approach was a median of 7% lower (range, 18% higher to 17% lower) than the corresponding fixed look-back approach, while the PPV was a median of 9% higher (range, 2% lower to 10% higher). One study compared multiple medication-on-hand approaches to pharmacists' expert opinion of each subject's active medications based on individualized review of each subject's pattern of medication dispensing but did not examine a separate source of medication use data.²⁰

4 | DISCUSSION

Our systematic review indicates that methods for establishing active medication lists using pharmacy databases have not been comprehensively validated in the literature, and while many approaches have been proposed, they have rarely been compared with one another. Pharmacy database approaches have primarily been validated against patient self-report of medication use, through interviews or surveys. The majority of studies are drawn from cohorts and intervention trials with complex inclusion criteria, which may not be generalizable to real-world medication use reporting or refill patterns. Prior studies have evaluated approaches using fixed look-back periods ranging from 12 weeks to 2 years and medication-on-hand approaches. While reported sensitivity ranged from 48% to 93% for fixed look-back period approaches and 35% to 96% for medication-on-hand approaches, interpretation of these results are limited by the use of heterogeneous pharmacy databases, populations, comparison metrics, and clinical settings.

As researchers increasingly investigate prescribing quality and the temporal relationship between medication use and clinical outcomes, there remains an urgent need for development and rigorous testing of pharmacy database approaches to identify active medications, and a clear understanding of the accuracy of these approaches in commonly used data sources. Our findings have immediate implications for pharmacoepidemiology and drug safety researchers seeking to determine cross-sectional drug exposure for which new-user cohort designs may not be feasible. While new-user cohort study designs are convenient for examining exposure to a single drug, this approach is not feasible for examining multiple drug classes (eg, studies of polypharmacy) or populations defined by a clinical event such as an adverse event or clinical encounter. For example, multiple prior case-control studies examining the association between drug exposures and hip fracture have used pharmacy databases to define active medication use.⁴¹⁻⁴³ In the absence of best practice, these studies have employed a wide range of active medication definitions: requiring one fill in the prior 30 days,⁴¹ one fill in the prior 180 days,⁴² and a medication-on-hand approach with a grace period equaling half of the days' supply.⁴³ This heterogeneity of approaches and the resultant differential misclassification may be one factor contributing to inconsistent observed associations. Thus, our review of the current literature raises several important themes, which may inform both future efforts to utilize pharmacy databases for studies of drug safety

and future studies seeking to validate algorithms for establishing active medication lists (Table 4).

First, it will be important to validate database algorithms by comparison with alternative sources of information on medication use. The consensus measures now routinely used for studies of adherence were the result of synthesis of studies comparing pharmacy database adherence algorithms to alternative sources of medication use information.^{4,5} Each comparison metric has important strengths and drawbacks. Patient interviews, the most common comparison in this review, are time intensive and susceptible to participation bias and recall errors. Patient surveys may suffer from low participation rates, unless included as part of routine clinical care.^{37,39} Biochemical measures are costly and may misclassify medication exposure for intermittently used medications or patients with transient nonadherence. Medication lists documented in electronic health records are likely to be of variable quality, as they may often reflect automated information populated from ordering systems which may not have been filled or may have been canceled. When available, medication reconciliation notes may provide a promising comparison, as they combine patient interviews conducted by clinicians, as part of regular clinical care, with a review of ordered prescriptions. However, it will be important for researchers to ensure the quality of these notes, which may also be impacted by the use of autopopulated medication lists from electronic health records and by experience of the person conducting the medication reconciliation, the information available to him or her, and by the degree of effort expended to obtain an accurate list.

Second, timeframe is likely the most important study design element in choosing algorithms for identifying active medications as this choice may directly impact the direction of potential misclassification bias. As depicted in Figure 2, the common approach of using a fixed look-back period may lead to both false positive and false negative classifications depending on the chosen look-back duration. Narrow look-back periods, such as 30 days, may miss active medications which were filled for extended supplies (eg, 90 days), medications used intermittently, medications taken with imperfect adherence, and medications which patients had stockpiled from prior fills. Conversely, broad look-back periods, such as 1 year, may classify medications no longer in use as active. The studies which compared different look-back periods consistently found that longer periods resulted in higher sensitivity but lower specificity and PPV.^{13,29,33,34} The second common approach identified in our review, the medication-on-hand approach, may improve upon fixed look-back period approaches by considering the days supplied in a fill, but may also misclassify active medications as nonactive, such as when patients fill medications late due to transient nonadherence or previous stockpiling of medications. The four studies to compare fixed look-back period approaches to medication-on-hand approaches found that medication-on-hand approaches were generally less sensitive but had a higher PPV than fixed look-back duration approaches.^{13-15,28} Investigators may consider adding grace periods to account for transient nonadherence^{6,44} as described in Figure 2. No studies directly compared the accuracy of medication-on-hand approaches with and without grace periods. Studies which considered fills following the index date were not directly compared with other approaches but risk misclassifying medications newly prescribed following the index date as active during the index date.

Third, future validation studies should pay careful attention to the scope of medications examined in pharmacy databases. As Goedken and colleagues have previously described, certain medication types are less likely to be included in pharmacy databases, such as over-the-counter medications, vitamins, and supplements.⁸ Pharmacy database approaches may need to be specified differently for medications used intermittently, those used with varying dosages (eg, insulin), and those used in nonstandardized dosage forms (eg, topical medications). Thus, a tailored rather than uniform approach to establishing active medications will likely be needed. The reviewed studies indicate that approaches with high sensitivity and specificity for chronic medications often have poorer accuracy for short duration and as-needed medications. Future validation studies might establish the accuracy of general approaches for broad medication categories, such as chronic prescribed medications versus as-needed medications, while individual research project goals should dictate which medications and methods are included in observational research studies.

Fourth, researchers should consider whether the pharmacy database of interest is likely to include all sources of medication of interest.⁴⁵⁻⁴⁷ In addition to nonprescription medications, prescriptions paid for with cash or using pharmaceutical samples may not be captured by certain pharmacy databases.^{48,49} Medications may not be captured by available claims data due to payment source, for example, Medicare Part D does not capture medications included as part of hospice care. Approaches for establishing active medication lists which have been validated in one database may not be as accurate in another, particularly when approaches validated in comprehensive national prescription registrars are extrapolated to more limited insurance or health system databases. This is particularly relevant in the United States, as we found few studies validating the use of Veterans Affairs, Medicare Part D, or private insurance databases, though all are commonly used in pharmacoepidemiology research. Consideration of site of care is important, as accuracy of approaches may differ in outpatient, nursing facility, and hospital settings. Medications used during hospital and skilled nursing facility stays may be supplied by internal pharmacies and thus not captured in other pharmacy databases.⁴⁵

Fifth, future validation efforts should seek to compare multiple pharmacy database approaches within the same cohort, as our findings indicate that comparing approaches across different cohorts in different settings and against different comparison groups provides limited generalizable knowledge. Beyond validation studies, for many research goals, there may be value in conducting sensitivity analyses comparing more and less restrictive approaches for identifying active medications in the same cohort. For example, researchers might use an extended fixed look-back period of 6 months to define possibly active medications in conjunction with a more restrictive medication-on-hand approach to define medications very likely to be in active use.

In conclusion, use of pharmacy databases to examine active medication use at specific time points is increasing as studies focusing on prescribing quality and clinical outcomes become more common. However, methods for establishing active medication lists using pharmacy databases have not yet been extensively assessed or validated in the literature. Researchers planning studies of cross-sectional medication exposure should carefully weigh the tradeoffs of aforementioned study design choices and must clearly define the approaches used in final

research products. Rigorous validation studies will be essential to establish best practices and improve the accuracy of measurement of active medication use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY POINTS

- Use of pharmacy databases to examine patients' medication use at specific time points is increasing, but few prior studies have systematically examined the validity of pharmacy database methods for establishing cross-sectional active medication lists.
- Pharmacy database algorithm sensitivity ranged from 48% to 93% for fixed look-back period approaches and 35% to 97% for medication-on-hand approaches.
- Interpretation of reported performance was limited by use of different nonpharmacy comparison metrics and lack of comparison of different pharmacy database approaches within study cohorts.
- There remains an urgent need for rigorous validation studies comparing pharmacy database approaches within and across study cohorts to establish best practices and improve the accuracy of measurement of cross-sectional active medication use.

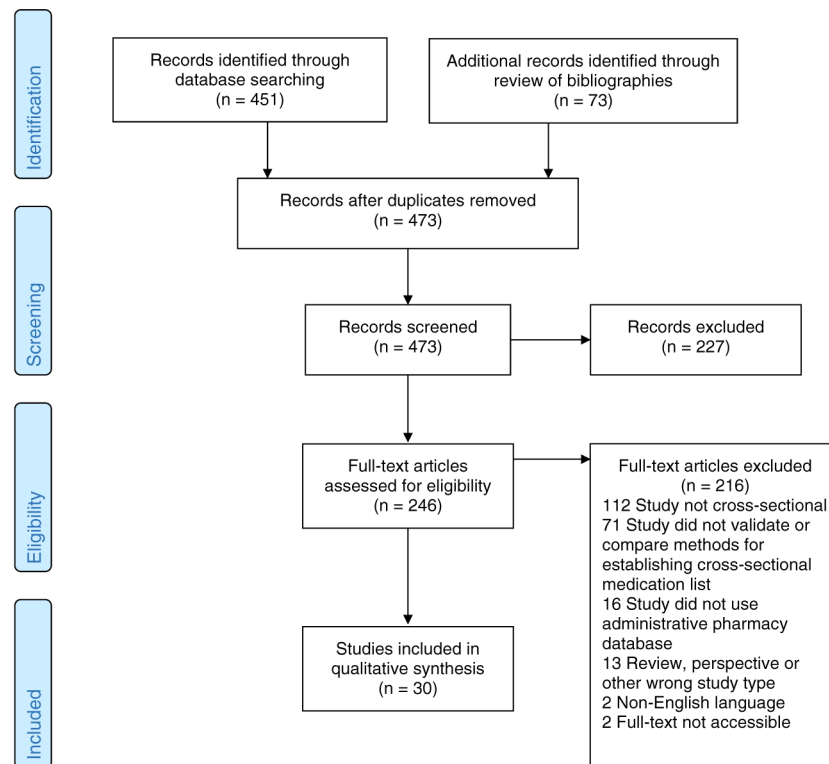


FIGURE 1. Systematic review PRISMA flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]

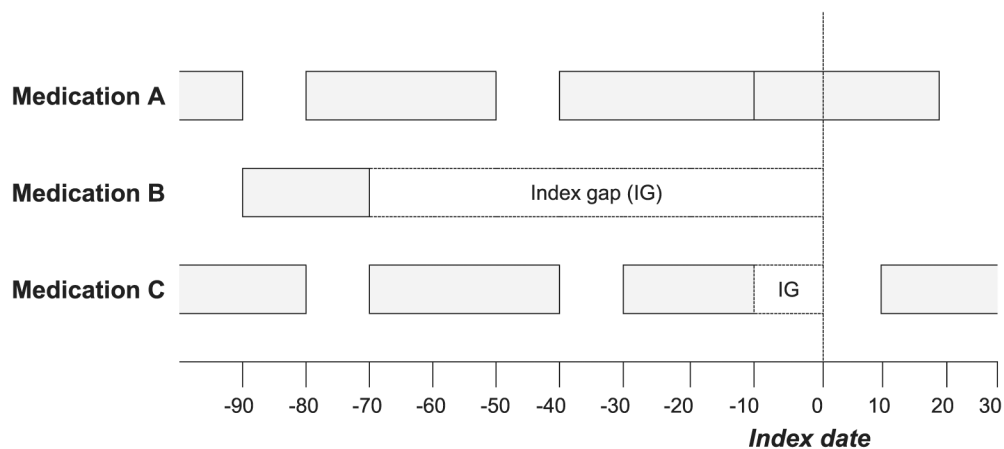


FIGURE 2.

Comparison of common approaches for establishing active medications at a fixed time point. In the above diagram, grey bars represent days supplied by medication fills in hypothetical refill patterns for three medications prescribed to a patient. The index gap (IG) is the period between the last day supplied by the most recent fill and the index date. Medication A has an index gap of 0 days, medication B has an index gap of 70 days, and medication C has an index gap of 10 days. Two common approaches to establishing an active medication list are demonstrated as follows:

1. Fixed look-back period approach: Defines active medications as those for which any fill occurred during a specified period prior to the index date. Using a fixed look-back period of 30 days would classify medications A and C as active, while using a fixed look-back period of 90 days would classify medications A, B, and C as active.
2. Medication-on-hand approach: Also termed legend duration approach. Defines active medications as those for which the most recent refill date provided sufficient supply to last through the study index date. Using this approach, only medication A would be classified as active. An allowable index gap may be added to the medication-on-hand approach, and would define active medications as those for which the most recent refill provided sufficient supply to last through the study index date including a grace period, which can be defined either as a fixed number of days or as a given percentage of the duration of the most recent fill. Using an allowable index gap of 14 days would classify medications A and C as active.

TABLE 1

Descriptive characteristics of included studies

Author, Publication Year	Country	Database Type	Database Name	Patient Population	Study Context	N	Comparison
Johnson, 1991 ¹¹	USA	Integrated health system pharmacy database	Kaiser Permanente	Adults age 65 enrolled in the health plan and reporting being bedbound or having 2 deficits in activities of daily living	All study respondents (response rate not listed)	83	Patient interview
Heerdink, 1995 ¹²	Netherlands	Single outpatient pharmacy	Not specified	Adults age 65 in one city district and who filled 1 prescription in the database in prior 6 months	Participants selected by general practitioners, selection approach not specified	100	Patient interview
Lau 1995 ¹³	Netherlands	Single outpatient pharmacy	Not specified	Adults age 70 who were either elder home residents or community dwelling in a single city district and who filled 1 prescription in the database in prior 6 months	Random sample recruited from participating general practices	115	Patient interview
Sjahidi, 1998 ¹⁴	Netherlands	Single outpatient pharmacy	Not specified	Adults age >55 in one city district	Participants in a prospective cohort study	1682	Patient interview
Klungel, 1999 ¹⁵	Netherlands	Regional network of community pharmacy databases	PHARMO database	Adults age 20-59 with hypertension from a single city district with available records in the PHARMO database	Survey respondents (response rate not listed)	372	Mailed survey
Lau, 2000 ¹⁶	Netherlands	Multiple individual outpatient pharmacy databases	Not specified	Adults age 40 hospitalized for 2 days in the general medicine ward of 2 hospitals with at 1 pharmacy fill in the prior year	Participants in a prospective cohort study	304	Chart review and patient survey
King, 2001 ¹⁷	Australia	National government pharmacy claims database	Australian pharmaceutical benefits scheme	Multicenter study of nursing home residents with evidence of 1 prescription in pharmacy claims database in prior year	All nursing home residents with eligible records	942	Chart review of nursing home records
Monster, 2002 ¹⁸	Netherlands	Multiple individual outpatient pharmacy databases	Not specified	Adults age 28-75 sampled from a single city	Survey participants (response rate 48%)	8592	In-clinic survey
Kwon, 2003 ¹⁹	USA	Managed care organization pharmacy database	Tufts health plan	Adults age 18 who screened positive for depression and were members of a single health plan	Randomized controlled trial participants	200	Mailed survey
Lund, 2003 ²⁰	USA	Regional government health system	Iowa Department of Health Services pharmacy claims	Community-dwelling adults with Medicaid, 1 chronic disease, and 4 medications	Random sample of participants in a pharmaceutical case management program	100	Pharmacist review of the pharmacy database ^a
Boudreau, 2005 ²¹	USA	Integrated health system pharmacy database	Group health cooperative	Community-dwelling adults age 67 with 1 chronic diseases and 2 years of health plan enrollment	Survey respondents (response rate 86%)	3610	Mailed survey
Caskie, 2006 ²²	USA	Integrated health system pharmacy database	Group health cooperative	Adults with available pharmacy data	Prospective study cohort participants	430	Patient interview

Author, Publication Year	Country	Database Type	Database Name	Patient Population	Study Context	N	Comparison
Curtis, 2006 ²³	USA	Managed care organization pharmacy database	Unspecified	Adults age 18 with chronic glucocorticoid use and enrolled in the health plan for 6 months	Survey respondents (response rate 38%)	2363	Mailed survey
Brown, 2007 ²⁴	USA	Integrated health system pharmacy database	Kaiser Permanente	Adults age 45 and members of a regional health plan	Prospective study cohort participants	7918	Patient interview
Glimborg, 2007 ²⁵	Denmark	National government pharmacy database	Danish Register of Medicinal Product Statistics	Single-center study of patients admitted to a general medicine ward	Prospective study cohort participants	500	Blood testing of drug levels
Haukka, 2007 ²⁶	Finland	National government pharmacy database	Finnish National Prescription Register	Participants from a population-based genetic study of schizophrenia	Retrospective cohort study participants	905	Patient interview
Shalansky, 2007 ²⁷	Canada	Regional government pharmacy database	PharmaNet (British Columbia)	Single-center study of patients with a clinic visit for heart failure OR prescribed one of three medications used for heart failure treatment	Interview participants (response rate 53%)	194	Patient interview
Nielsen, 2008 ²⁸	Denmark	National government pharmacy database	Danish Register of Medicinal Product Statistics	Adults age 16	Survey respondents (response rate 74%)	16 688	Patient interview
Pit, 2008 ²⁹	Australia	National government pharmacy claims database	Australian Pharmaceutical Benefits Scheme	Adults age 65 attending 20 general practice clinics	Randomized controlled trial participants	566	Patient interview
Warholak, 2009 ³⁰	USA	Aggregated pharmacy claims database from multiple pharmacy benefit managers	RxAccord	Hospitalized adults age 18 enrolled in participating insurance plan	Random sample	78	Chart review of admission medication list
Noize, 2009 ³¹	France	National government pharmacy database	CNAM-TS	Community-dwelling adults age 67 from 3 French cities	Prospective cohort participants with available pharmacy data (44% of cohort)	4112	Patient interview with examination of drug packaging
Haapea, 2010 ³²	Finland	National government pharmacy database	Finnish National Prescription Register	Patients born in 2 Finnish provinces in 1966 and alive in 1997	Survey respondents (response rate 66%)	7625	Mailed survey
Rikala, 2010 ³³	Finland	National government pharmacy database	Finnish National Prescription Register	Adults age 75 in a single city	Randomized controlled trial participants and agreeing to follow-up study	570	Patient interview
Allin, 2013 ³⁴	Canada	Regional government pharmacy database	Ontario Drug Benefit Program	Community-dwelling adults age 65	Survey respondents (response rate not listed)	32 848	Patient interview
Richardson, 2013 ³⁵	Ireland	National government pharmacy database	Health Service Executive-Primary Care Reimbursement Services	Community-dwelling adults age 50 and providing consent for pharmacy linkage	Participants in an observational cohort study (response rate 62%)	2621	Patient interview
Fujita, 2015 ³⁶	Japan	Regional government pharmacy database	National Health Insurance of Chiba City	Adults age 40-74	All adults receiving a regular check up	54 712	Chart review of questionnaire used in routine clinic practice

Author, Publication Year	Country	Database Type	Database Name	Patient Population	Study Context	N	Comparison
Colantonio, 2016 ³⁷	USA	National government pharmacy database	Medicare part D	Adults age 45 receiving Medicare pharmacy benefits	Participants in a national population-based observational cohort study	899	Telephone survey and patient interview with examination of drug packaging
Drieling, 2016 ³⁸	USA	Integrated health system pharmacy database	Group Health Cooperative	Women age 60, participating in a longitudinal cohort study, and enrolled in the same health plan for 5 years	Survey respondents (response rate 48%)	223	Mailed survey
Lacasse, 2016 ³⁹	Canada	Regional government pharmacy database	Regie de l'assurance Maladie du Quebec (RAMQ)	Adults 18 seen in participating chronic pain clinics with records in the pharmacy database in the prior year	Study respondents (response rate 44%)	272	Chart review of questionnaire used in routine clinic practice
Taipale, 2016 ⁴⁰	Finland	National government pharmacy database	Finnish National Prescription Register	Community-dwelling adults age 75 from a single city	Randomized controlled trial participants	569	Patient interview

⁴Lund (2013) compared active medication lists generated by the pharmacy database algorithms to active medication lists generated by pharmacist review of the same pharmacy review database; no alternative source of medication use data was examined.

TABLE 2

Definition of active medications using pharmacy records

Author, Year	Version ^a	Scope	Index Date	Criteria for Active Medications Using Pharmacy Database
Fixed look-back period approaches				
Johnson, 1991 ¹¹	-	18 medication classes	Interview date	Any fills in the 90 days prior to index date.
Heerdink, 1995 ¹²	-	All medications	Interview date	Any fills in the 2 years prior to index date.
Lau, 1995 ¹³	A	8 medication classes	Interview date	Any fills in the 90 days prior to index date.
	B	8 medication classes	Interview date	Any fills in the 30 days prior to index date.
Sjahid, 1998 ¹⁴	A	8 cardiac medication classes	Interview date	Any fills in the 6 months prior to index date.
Klungel, 1999 ¹⁵	A	Antihypertensive medications	Date of survey completion	Any fills in available records. Range 90 days to 16 months prior to index date.
King, 2001 ¹⁷	-	All medications	Date of nursing home visit	Any fills in the 12 weeks prior to index date.
Monster, 2002 ¹⁸	-	7 medication classes	Date of survey completion	Any fills in the 1 year prior to index date.
Kwon, 2003 ¹⁹	-	Antidepressant medications	Date of survey completion	Any fills in the 90 days prior to index date.
Curtis, 2006 ²³	-	Osteoporosis medications	Date of survey completion	Any fills in the 180 days prior to index date.
Glintborg, 2007 ²⁵	-	5 medications	Date of hospital admission	Any fills in the 6 month prior to index date.
Haukka, 2007 ²⁶	-	8 psychotropic medication classes	Interview date	Any fills in the 6 months prior to index date.
Nielsen, 2008 ²⁸	A	16 medication classes	Interview date	Any fills in the 90 days prior to index date.
Pit, 2008 ²⁹	A	6 medication classes and 3 individual medications	Interview date	Any fills in the 30 days prior to index date.
	B	6 medication classes and 3 individual medications	Interview date	Any fills in the 60 days prior to index date.
	C	6 medication classes and 3 individual medications	Interview date	Any fills in the 90 days prior to index date.
	D	Benzodiazepines and NSAIDS	Interview date	Any fills in the 180 days prior to index date.
	E	Benzodiazepines and NSAIDS	Interview date	Any fills in the 365 days prior to index date.
Noize, 2009 ³⁰	-	38 medication classes	Interview date	Any fills in the 60 days prior to index date.
Haapae, 2010 ³²	-	5 medication classes	Date of survey completion	Any fills in the 6 months prior to index date.
Rikala, 2010 ³³	A	3 classes of psychotropic medications	Interview date	Any fills in the 4 months prior to index date.
	B	3 classes of psychotropic medications	Interview date	Any fills in the 6 months prior to index date.
	C	3 classes of psychotropic medications	Interview date	Any fills in the 1 year prior to index date.

Author, Year	Version ^a	Scope	Index Date	Criteria for Active Medications Using Pharmacy Database
Allin, 2013 ³⁴	A	Antihypertensives and oral diabetes medications	Interview date	Any fills in the 30 days prior to index date.
	B	Antihypertensives and oral diabetes medications	Interview date	Any fills in the 100 days prior to index date.
	C	Antihypertensives and oral diabetes medications	Interview date	Any fills in the 130 days prior to index date.
Richardson, 2013 ³⁵	-	19 medication classes	Interview date	3 Fills in the 6 months prior to index date and 1 fill in the 1 month prior to index date
Colantonio, 2016 ³⁶	A	Lipid-lowering medications	Phone interview date	Any fills in the 120 days prior to index date.
	B	Lipid-lowering medications	In-person interview date	Any fills in the 120 days prior to index date.
Lacasse, 2016 ³⁹	-	8 classes of analgesic medications	Date of questionnaire completion	Any fills in the 1 year prior to index date.
Medication-on-hand (legend duration) approaches				
Lau, 1995 ¹³	C	8 medication classes	Interview date	Index date falls within the period from the [fill date] for a medication through the [fill date] + 110% of the days' supply].
Sjahid, 1998 ¹⁴	B	All cardiovascular medications	Interview date	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply].
Klungel, 1999 ¹⁵	B	Antihypertensive medications	Date of survey completion	Index date falls within the period from the [fill date] for a medication through the [fill date] + 110% of the days' supply].
Lau, 2000 ¹⁶	-	All medications	Interview date	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply + 7-day grace period].
Lund, 2003 ²⁰	A	All medications	October 1, 2000	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply].
	B	All medications	October 1, 2000	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply] AND there is a fill both before and after the index date with a time period between fills of <90 days.
	C	All medications	October 1, 2000	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply] AND there is a fill both before and after the index date with a time period between fills of <90 days. PLUS: A fill is required within 90 days before the index date for as-needed medications only.
	D	All medications	October 1, 2000	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply] AND there is a fill both before and after the index date with a time period between fills of <90 days. PLUS: For as needed medications, there is a fill both 180 days before the index date AND 60 days after the index date.
Boudreau, 2005 ²¹	-	7 medication classes	Date of survey completion	At least 2 prescriptions for the medication were filled in the 12 months prior to index date AND the index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply + 60-day grace period].
Caskie, 2006 ²²	-	16 medication classes	Interview date	Index date falls within the period from the [fill date] for a medication through the [fill date] + days' supply + 7-day grace period]. For anti-infective medications only the grace period was 2 days rather than 7 days.

Author, Year	Version ^a	Scope	Index Date	Criteria for Active Medications Using Pharmacy Database
Shalansky, 2007 ²⁷		All medications	Interview date	Index date falls within the period from the [fill date] for a medication through the [fill date + days' supply].
Nielsen, 2008 ²⁸	B	16 medication classes	Interview date	Index date falls within the period from the [fill date] for a medication through the [fill date + 110% of the days' supply].
Warholak, 2009 ³⁰	-	All medications	Date of hospital admission	Index date falls within the period from the [fill date] for a medication through the [fill date + days' supply].
Drieling, 2016 ³⁸	-	4 medication classes	Date of survey completion	Index date falls within the period from the [fill date] for a medication through the [fill date + day's supply] OR gap of <60 days was present between the most recent preindex [fill date + days' supply] and the first postindex fill.
Other approaches				
Brown, 2007 ²⁴	A	Lipid-lowering medications	Interview date	Any fills in the 15 days before or after the index date
	B	Lipid-lowering medications	Interview date	Any fills in the 30 days before or after the index date
	C	Lipid-lowering medications	Interview date	Any fills in the 60 days before or after the index date
	D	Lipid-lowering medications	Interview date	Any fills in the 90 days before or after the index date
Fujita, 2015 ³⁷	A	Hypertension, diabetes, and lipid-lowering medications	Date of clinic visit	Any fills in the same month as the index date
	B	Hypertension, diabetes, and lipid-lowering medications	Date of clinic visit	Any fills in 2 months prior or the same month as the index date
Taipale, 2016 ⁴⁰	-	34 medication classes	Interview date	Variable and based on mathematical modeling of personal medication purchasing behaviors (PRE2DUP model)

^aThe following studies compared multiple approaches using different criteria to define active medications using pharmacy databases, noted by the version A-D: Lau (1995), Sjahid (1998), Klungel (1999), Nielsen (2008), Pit (2008), Rikala (2010), Allin (2013), Lund (2003), Brown (2007), and Fujita (2015). King (2001), Curtis (2006), Haukka (2007), and Noize (2009) also examined alternative approaches for defining active medications; however, the manuscripts only reported numeric results for the approaches listed in the tables.

TABLE 3

Results of studies comparing pharmacy records to other sources of active medication lists

Author, Year	Version ^a	Pharmacy Database Criteria for Active Medications	Comparison	Sens.	Spec.	PPV	NPV	Kappa	PABAK
Fixed look-back period approaches									
Johnson, 1991 ¹¹	-	Any fills in the 90 days prior to index date.	Patient interview	50-100 (Median 80)	88-100 (Median 96)	22-100 (Median 82)	-	-	-
Heerdink, 1995 ¹²	-	Any fills in the 2 years prior to index date.	Patient interview	79	-	-	-	-	-
Lau, 1995 ¹³	A	Any fills in the 90 days prior to index date	Patient interview	69-100 (Median 82)	88-100 (Median 99)	19-100 (Median 90)	-	-	-
Sjahid, 1998 ¹⁴	A	Any fills in the 30 days prior to index date	Patient interview	38-73 (Median 50)	93-100 (Median 100)	33-100 (Median 100)	-	-	-
King, 2001 ¹⁷	A	Any fills in the 6 months prior to index date.	Patient interview	93	-	85	-	0.36-0.97 (Median 0.91)	-
Klungel, 1999 ¹⁵	A	Any fills in available records. Range 90 days to 16 months prior to index date.	Mailed patient survey	93	91	90	94	0.89	0.89
King, 2001 ¹⁷	A	Any fills in the 12 weeks prior to index date.	Chart review of nursing home records	78	-	60	-	-	-
Monster, 2002 ¹⁸	B	Any fills in the 12 weeks prior to index date.	Chart review of nursing home records	48	-	56	-	-	-
Kwon, 2003 ¹⁹	-	Any fill in the 1 year prior to index date.	Patient survey	54	96	64	94	0.53	0.81
Curtis, 2006 ²³	-	Any fills in the 90 days prior to index date.	Mailed patient survey	90	82	74	94	0.69	0.7
Glintborg, 2007 ²⁵	-	Any fills in the 180 days prior to index date.	Mailed patient survey	68	99	90	98	0.76	0.95
Haukka, 2007 ²⁶	-	Any fills in the 2 years prior to index date.	Blood testing of drug levels	93	-	-	-	-	-
Nielsen, 2008 ²⁸	A	Any fills in the 6 months prior to index date.	Patient interview	71	99	90	96	0.77	0.91
Nielsen, 2008 ²⁸	A	Any fills in the 90 days prior to index date.	Patient interview	79	98	55	99	0.64	0.95

Author, Year	Version ^a	Pharmacy Database Criteria for Active Medications	Comparison	Sens.	Spec.	PPV	NPV	Kappa	PABAK
Pit, 2008 ²⁹	A	Any fills in the 30 days prior to index date.	Telephone interview	33-81 (Median 60)	96-100 (Median 99)	81-100 (Median 93)	69-98 (Median 91)	-	0.62-0.97 (Median 0.83)
	B	Any fills in the 60 days prior to index date.	Telephone interview	54-93 (Median 78)	91-100 (Median 97)	71-100 (Median 90)	86-98 (Median 96)	-	0.74-0.98 (Median 0.89)
	C	Any fills in the 90 days prior to index date.	Telephone interview	71-100 (Median 83)	86-100 (Median 96)	64-97 (Median 90)	90-100 (Median 97)	-	0.71-1.00 (Median 0.90)
	D	Any fills in the 180 days prior to index date.	Telephone interview	83-89 (Median 86)	78-95 (Median 87)	54-66 (Median 60)	96-98 (Median 97)	-	0.61-0.88 (Median 0.75)
	E	Any fills in the 365 days prior to index date.	Telephone interview	90-95 (Median 93)	66-92 (Median 79)	45-57 (Median 51)	98-99 (Median 98)	-	0.45-0.84 (Median 0.65)
Noize, 2009 ³¹	-	Any drug reimbursement claims in the 60 days prior to index date.	Patient interview with examination of drug packaging	1-91 (Median 73)	81-100 (Median 99)	14-100 (Median 79)	76-100 (Median 97)	0.02-0.93 (Median 0.69)	-
Haapae, 2010 ³²	-	Any fills in the 6 months prior to index date.	Mailed patient survey	74	99	71	99	0.72	0.99
Rikala, 2010 ³³	A	Any drug reimbursement claims in the 4 months prior to index date	Patient interview	70	98	87	94	0.73	0.85
	B	Any drug reimbursement claims in the 6 months prior to index date	Patient interview	78	97	86	95	0.77	0.87
	C	Any drug reimbursement claims in the 12 months prior to index date	Patient interview	84	96	82	96	0.79	0.87
Allin, 2013 ³⁴	A	Any fills in the 30 days prior to index date.	Patient interview	-	-	32-47 (Median 37)	91-99 (Median 95)	0.24-0.55 (Median 0.38)	-
	B	Any fills in the 100 days prior to index date.	Patient interview	-	-	70-86 (Median 79)	78-99 (Median 89)	0.46-0.87 (Median 0.67)	-
	C	Any fills in the 130 days prior to index date.	Patient interview	-	-	73-88 (Median 83)	77-99 (Median 89)	0.47-0.89 (Median 0.68)	-
Richardson, 2013 ³⁵	-	3 fills in the 6 months prior to index date and 1 fill in the one month prior to index date.	Patient interview	78	96	76	96	0.73	0.86
Colantonio, 2016 ³⁶	A	Any fills in the 120 days prior to index date.	Phone interview	78	90	86	86	0.72	0.73

Author, Year	Version ^a	Pharmacy Database Criteria for Active Medications	Comparison	Sens.	Spec.	PPV	NPV	Kappa	PABAK
	B	Any fills in the 120 days prior to index date.	Interview with examination of drug packaging	81	90	86	87	0.68	0.69
Lacasse, 2016 ³⁹	-	Any fills in the 365 days (1 year) prior to index date.	Patient questionnaire used in routine clinic practice	53-100 (Median 78)	63-99 (Median 93)	27-81 (Median 74)	84-100 (Median 95)	0.11-0.83 (Median 0.66)	
Medication-on-hand approaches									
Lau, 1995 ¹³	C	Index date falls within the period from the [fill date] for a drug through the [fill date + 110% of the days' supply].	Patient interview	69-100 (Median 78)	93-100 (Median 100)	84-100 (Median 100)	-	-	-
Sjahidi, 1998 ¹⁴	B	Index date falls within the period from the [fill date] for a drug through the [fill date + days' supply].	Patient interview	85	-	94	-	0.27-0.97 (Median 0.89)	-
Klungel, 1999 ¹⁵	B	Index date falls within the period from the [fill date] for a drug through the [fill date + 110% of the days' supply].	Mailed patient survey	76	91	88	82	0.67	0.68
Lau, 2000 ¹⁶	-	Index date falls within the period from the [fill date] for a drug through the [fill date + days' supply + 7-day grace period].	Patient questionnaire and hospital medical record	89	-	93	-	-	-
Lund, 2003 ²⁰	A	Index date falls within the period from the [fill date] for a medication through the [fill date + days' supply].	Pharmacist review of the pharmacy database	78	99	-	-	-	-
	B	Index date falls within the period from the [fill date] for a medication through the [fill date + days' supply] AND there is a fill both before and after the index date with a time period between fills of <90 days.	Pharmacist review of the pharmacy database	92	96	-	-	-	-
	C	Index date falls within the period from the [fill date] for a medication through the [fill date + days' supply] AND there is a fill both before and after the index date with a time period between fills of <90 days. PLUS: A fill is required within 90 days before the index date for as-needed medications only.	Pharmacist review of the pharmacy database	94	92	-	-	-	-
	D	Index date falls within the period from the [fill date] for a medication through the [fill date + days' supply] AND there is a fill both before and after the index date with a time period between fills of <90 days. PLUS: For as needed medications, there is a fill both 180 days before the index date AND 60 days after the index date.	Pharmacist review of the pharmacy database	94	92	-	-	-	-
Boudreau, 2005 ²¹	-	At least 2 prescriptions for the medication were filled in the 12 months prior to index date AND the index date falls within the period from the [fill date]	Patient mailed survey	-	-	-	-	0.43-0.88 (Median 0.81)	0.51-0.92 (Median 0.88)

Author, Year	Version ^a	Pharmacy Database Criteria for Active Medications	Comparison	Sens.	Spec.	PPV	NPV	Kappa	PABAK
Caskie, 2006 ²²	-	for a drug through the [fill date + days' supply + 60-day grace period].	Patient interview	38-82	89-100	-	-	0.00-0.92	-
Shalansky, 2007 ²⁷	-	Index date falls within the period from the [fill date] for a drug through the [fill date + days' supply + 7-day grace period].	Patient interview	84	-	97	-	-	-
Nielsen, 2008 ²⁸	B	Index date falls within the period from the [fill date] for a drug through the [fill date + 110% of the days' supply].	Patient interview	68	99	65	99	0.65	0.96
Warholak, 2009 ³⁰	-	Index date falls within the period from the [fill date] for a drug through the [fill date + days' supply].	Chart review of admission medication list	35	-	24	-	-	-
Drieling, 2016 ³⁸	-	Index date falls within the period from the [fill date] for a drug through the [fill date + days' supply] OR gap of 60 days was present between the most recent preindex [fill date + days' supply] and the first postindex fill.	Mailed patient survey	96	99	98	99	0.96	0.97
Other approaches									
Brown, 2007 ²⁴	A	Any fills in the 15 days before or after the index date	Patient interview	21	99	98	93	-	-
	B	Any fills in the 30 days before or after the index date	Patient interview	35	99	96	95	-	-
	C	Any fills in the 60 days before or after the index date	Patient interview	54	99	94	97	0.67	0.92
	D	Any fills in the 90 days before or after the index date	Patient interview	59	99	91	96	-	-
Fujita, 2015 ³⁷	A	Any fills in the same month as the index date	Patient questionnaire used in routine clinic practice	56	98	90	90	0.63	0.79
	B	Any fills in 2 months prior or the same month as the index date	Patient questionnaire used in routine clinic practice	69	98	89	93	0.73	0.84
Taiplae, 2016 ⁴⁰	-	Variable and based on mathematical modeling of personal drug purchasing behaviors (PREZDUP model)	Patient interview	82	99	93	97	0.85	0.93

Abbreviations: PABAK, prevalence-adjusted and bias-adjusted kappa; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.

^aThe following studies compared multiple approaches using different criteria to define active medications using pharmacy databases, noted by the version A-D: Lau (1995), Sjahid (1998), Klungel (1999), Nielsen (2008), Pit (2008), Rikala (2010), Allin (2013), Lund (2003), Brown (2007), and Fujita 2015.

TABLE 4

Considerations for designing and validating studies using administrative pharmacy records to identify active medication at a fixed time point

Comparison group for validation studies	• Is the proposed study design prospective or retrospective?
	• If prospective options include: <ul style="list-style-type: none"> – Biochemical markers – Patient interview – Patient survey – Medication reconciliation (patient interview guided by clinician and based upon existing medical record medication list)
	• If retrospective options include: <ul style="list-style-type: none"> – Biochemical markers (may be retrospectively collected if ordered as part of routine clinical care) – Electronic medical record – Patient survey (if part of routine clinical care, such as patient intake during a clinic visit) – Medication reconciliation (may be retrospective if completed as part of routine clinical care such as during new patient visits or hospital admission)
	• What will the primary method for identifying active medications? (Figure 2) <ul style="list-style-type: none"> – Use of fixed look-back period approaches requires a decision on how far before the index date a medication can be filled to be counted as active. Longer look-back periods may classify medications no longer in use as active while shorter look-back periods may miss medications filled intermittently or with extended supplies. – Use of medication-on-hand approaches may be limited for medications without a recorded day supplied, medications with nonstandard dosage forms, and those used intermittently
	• If a fixed look-back period approach is used, will multiple preindex date fills be required or minimum days' supply?
Scope of medications	• If a medication-on-hand approach is used, will a grace period be included to account imperfect adherence or refill delays?
	• Will postindex date fills be considered?
	• Are nonprescription medications, supplements, and vitamins important to the research question?
	• Does the pharmacy database record fills of nonprescription medications, supplements, or vitamins?
	• Will a different approach be used for examining as-needed medications which may not be filled at regular intervals?
Medication sources	• Will a different approach be used for examining medications used for a short duration (eg, antibiotics) which may not be filled at regular intervals?
	• Will a different approach be used to examine medications with nonstandard dosage forms (eg, topical/inhaled/injection medications) for which days' supply may not be readily measurable?
	• Is the pharmacy database being used likely to include all medications being taken by the study population? <ul style="list-style-type: none"> – Is the patient likely to obtain prescriptions from another source not captured by the database? – Prescriptions filled with cash, no-charge, and drug coupons may not be recorded in many pharmacy databases.

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– Recent hospitalization, residence in a skilled nursing facility, and incarceration may result in medication provided by alternative pharmacy sources or not captured in claims data.

• Would study findings be strengthened by comparing multiple approaches for establishing patients' active medication list?

Multiple measures