Received: 1 November 2021 | Revised: 1 June 2022 | Accepted: 3 June 2022

DOI: 10.1002/pds.5490

WILEY

Core concepts in pharmacoepidemiology: Measures of drug utilization based on individual-level drug dispensing data

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Abstract

Background: Drug utilization studies are essential to facilitate rational drug use in the society.

Aim: In this review, we provide an overview of drug utilization measures that can be used with individual-level drug dispensing data, referencing additional reading on the individual analysis. This is intended to serve as a primer for those new to drug utilization research and a shortlist from which researchers can identify useful analytical approaches when designing their drug utilization study.

Results and Discussion: We provide an overview of: (1) basic measures of drug utilization which are used to describe changes in drug use over time or compare drug use in different populations; (2) treatment adherence measures with specific focus on persistence and implementation; (3) how to measure drug combinations which is useful when assessing drug–drug interactions, concomitant treatment, and polypharmacy; (4) prescribing quality indicators and measures to assess variations in drug use which are useful tools to assess appropriate use of drugs; (5) proxies of prescription drug misuse and skewness in drug use; and (6) considerations when describing the characteristics of drug users or prescribers.

KEYWORDS
databases, drug utilization, incidence, medication adherence, pharmacoepidemiology, prescribing patterns, prevalence

Key Points

- Drug utilization studies facilitate rational use of drugs in the society by documenting who uses and who prescribes drugs, why the drug is prescribed and how it is used, and whether there are differences in drug use over time, between practices, populations, regions, or countries.
- Incidence and prevalence are basic epidemiological measures of drug use that can be used to study the year-on-year development in a populations' use of a drug, to compare drug use between populations or countries, or to estimate under- or over-prescribing of a drug in a population.
- Adherence to medications, that is, persistence and implementation, can be studied using individual-level drug dispensing data and common methods include the refill gap method, the

anniversary model, the proportion of days covered, and the medication possession ratio. It is often relevant to study both persistence and implementation.
- Individual-level drug dispensing data can be used to assess drug combinations (concurrent drug use, polypharmacy, and drug–drug interactions) and switching. However, it is often difficult to distinguish combination use from switching and the risk of misclassification should be kept in mind.
- Individual-level drug dispensing data can be used to assess prescription drug misuse. The four most common proxies include the number of prescribers, the number of pharmacies dispensing the drug, overlapping prescriptions, and the volume of dispensed drug.

1 | INTRODUCTION

Drug utilization studies are essential to facilitate and promote rational drug use in the society. They mainly do so by identifying areas of concern which may then lead to risk minimization measures aiming to ensure the rational use of drugs. Drug utilization studies may focus on questions of who uses the drug, who prescribes the drug, why is the drug prescribed, is the drug used as prescribed, and are there differences in drug use over time, between practices, populations, regions, or countries.[1]

Drug utilization data may be collected from wholesalers, electronic health records, pharmacies, or patients, with the availability of such data varying considerably between countries. In many settings, data are kept by healthcare providers and payers, for example, national health services, insurance companies or reimbursement agencies, and the access to data for research and practice may vary substantially. Data may be either aggregated or collected at the individual level, the latter often including a unique identifier on the single drug user. By using routinely collected individual-level drug prescribing or dispensing data, it is possible to describe basic measures of drug utilization such as incidence and prevalence of drug use and more advanced measures such as treatment adherence, drug combinations, drug switching, concurrent drug use, polypharmacy, and potential prescription drug misuse or skewed distribution in the total prescribed or dispensed drug volume among those using the drug. In addition, individual-level drug prescribing or dispensing data may also be linked with data on diagnoses or socioeconomic status to comprehensively characterize drug users or to assess outcomes of the therapy. Finally, individual-level drug prescribing or dispensing data may be used to assess variations in drug use between populations or to construct prescribing quality indicators (PQIs) to assess appropriate use of drugs.

Drug utilization studies thus constitute an important discipline within pharmacoepidemiology in describing, analyzing, and understanding patterns of drug use and in estimating the population at risk when a safety issue of a medication is identified. In this review, we provide an overview of different measures of drug utilization for studies based on individual-level drug dispensing data, also providing reference to suggested further reading. This is intended both as a primer for new researchers in pharmacoepidemiology and its nomenclature (Table 1) and as a list to revisit for inspiration when planning a new drug utilization study. For a broader introduction to drug utilization measures and drug utilization research in general we recommend the textbook "Drug Utilization Research Methods and Applications" by Elseviers et al.[1]

2 | DATA SOURCES ON INDIVIDUAL-LEVEL DRUG USE

There are hundreds of available data sources containing individual-level data describing use of drugs, for example, the Nordic prescription registries which are based on pharmacy dispensing data, the Clinical Practice Research Datalink (CPRD) which is a UK primary care data source including prescription data, or the IMS LifeLink Health Plans Claims Database which is based on US reimbursement data, and so forth. Individual-level data sources on dispensed drugs contain data on the single drug user and allows detailed assessment of an individual's history of dispensed drugs. In some individual-level databases, data on dispensed drugs may be linked to separate patient-level databases to obtain information on, for example, diagnoses, socioeconomic status, or population death statistics. In other databases, such data are already included. Some databases contain all dispensed prescription drugs, while others are restricted to drugs financed by reimbursement systems and thus do not contain drugs paid for out of the pocket. A general limitation for many individual-level drug dispensing databases is the lack of data on over the counter (OTC) medications and drugs administered in the hospital setting.

2.1 | The Anatomical Therapeutic Chemical and Defined Daily Doses

In many databases, drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification system, and drug volume is expressed as Defined Daily Doses (DDD). Of note, some data sources do not use the ATC system, for example, US data sources using National Drug Codes and UK data sources using Read codes. Both the ATC and the DDD system are developed and maintained by the World Health Organization (WHO). The DDD is a standardized measure of drug volume based on the "assumed average maintenance dose per day for a drug used for its main indication in adults."[2] As the

TABLE 1 Important terms and definitions in drug utilization research

	Definition/explanation
Defined daily dose (DDD)[2]	"…the assumed average maintenance dose per day for a drug used for its main indication in adults.".
ATC code[2]	A code used to classify drugs according to their therapeutic and chemical properties.
Incidence	The rate of new users over time calculated by dividing the number of new drug users by the person-time at risk.
Person-time	The total sum of follow-up time in a population often expressed in years.
Wash-out period	A period in which there is no dispensing (used to define "new use" in incidence measures).
Prevalence	The proportion of existing drug users calculated by dividing the number of current drug users by the total population count.
Prescribed daily dose	The drug amount to be taken daily according to dosing instructions.
Adherence[4]	"…the process by which patients take their medications as prescribed.".
Initiation	The extent to which patients start using the medication.
Persistence	The time from initiation of treatment and until discontinuation.
Implementation	The extent to which a patient's actual dosing corresponds to the prescribed daily dose.
Grace period	A permissible gap between prescriptions which is applied in persistence measures to allow for late prescription refills and stockpiling.
Stockpiling	Oversupply of medication due to overlapping prescriptions.
Prescribing quality indicators (PQIs)[40]	"…a measurable element of prescribing performance for which there is evidence or consensus that it can be used to assess quality, and hence in changing the quality of care provided.".
Doctor-shopping	The consulting of multiple prescribers to receive prescriptions of the same medication.

DDD reflects the daily maintenance dose for its main indication in adults, this should be considered for drugs with multiple indications where different dosages are used such as, for example, amitriptyline which is used in higher dosages in, for example, depression compared to neuropathic pain. DDDs are valuable tools to describe aggregate drug use when there is no individual-level drug dispensing data available, since the amount of DDDs sold can estimate the number of users. The amount of DDDs sold in a geographic area may be assessed in relation to the time window and population size to calculate the number of DDDs/1000 inhabitants per day (DDD/TID). Correspondingly, sales data for hospitals can be adjusted for time, number of beds and occupancy to the measure DDD/100 bed-days. Importantly, the DDD is not the clinically recommended therapeutic dose but solely a unit of measurement which means that it does not necessarily reflect actual use. This is important to keep in mind when interpreting drug utilization figures in children or elderly as this could lead to an underestimate of the number of drug users if, in the case of children, there is no pediatric formulation. The ATC and DDD may change over time and therefore researchers are recommended to refer to the ATC/DDD version used in their current study. For further reading on the ATC classification and DDD assignment, we refer to the WHO Collaborating Centre for Drug Statistic (WHOCC) webpage (https://www.whocc.no/) and the most current WHOCC Guidelines for ATC classification and DDD assignment.[2]

3 | BASIC EPIDEMIOLOGICAL MEASURES OF DRUG USE

Basic epidemiological measures of drug use include measures of incidence and prevalence of drug use. These measures of drug utilization are relevant in almost any drug utilization study and are especially useful in studies where the main aim is to compare drug use over time or between different countries, regions, or populations. Furthermore, prevalence of drug use may be compared with disease prevalence to give a crude estimate of under- or over-prescribing in a population or to estimate the population at risk if a safety issue of a medication is identified.

3.1 | Measuring incidence of drug use

The incidence rate is the rate of new drug users, defined as the number of new drug users in a period of time divided by the sum of the person-time at risk in the same period. The person-time reflects the sum of the individual follow-up time, for example both 1000 persons followed for 1 year, or 500 persons followed for 2 years correspond to 1000 person-years. An example of an incidence rate is: "50 new drug users per 10 000 person-years." Often, the total population follow-up may be used as the denominator as an approximation of the person-time at risk when the number of new drug users is negligible compared to the total population. The definition of "new use" can vary between studies depending on how long time-series of data that are available. For example, this could be based on all data available or the last 10, 5, or 2 years of data. The choice of a so-called wash-out-period, that is, the period in which no dispensing may have happened in order to qualify the recent prescription fill as "new use," also vary depending on the type of drugs that are being assessed, for example, chronic therapy such as cardiovascular drugs versus short term-therapy such as antibiotics or analgesics. Another incidence measure is the cumulative incidence or incidence proportion, commonly referred to as risk. This is the proportion of new drug users divided by the size of the untreated population at the beginning of the

observation window. This could be a 1-year risk of 12% of starting cardiovascular medication among elderly.

3.2 | Measuring prevalence of drug use

There are two commonly used prevalence measures: the point prevalence and the period prevalence. The period prevalence is the most commonly used in drug utilization studies and describes the proportion of a population that are users of a drug at some point during a specific period, often a year. The numerator thus includes both new users and continuous (prevalent) drug users, while the total population is used as denominator. As such, the prevalence is a mixture of both existing drug users and new drug users. An example which uses a period prevalence is: "the proportion of the population filling at least one prescription for a proton pump inhibitor in 2020 was 10%." The point prevalence similarly describes the proportion of a population using the drug, however, at a specific point in time (e.g., "7% of the population used a proton pump inhibitor on January 1st, 2020"). Although some individual-level databases on drug use contains a "days' supply" variable (e.g., US data sources), many individual-level drug dispensing databases do not contain this information. Hence, when using databases without this information, estimates of point prevalence is often based on strong assumptions about the prescribed daily dose and the prescription duration. Importantly, when reporting and interpreting period prevalences, it is important to keep in mind that the period prevalence estimates the number of drug users over a period of time. Thus, depending on the length of this period and the duration of drug treatment, estimates of a period prevalence will be higher than the number of drug users on a specific day. Consider the example where the number of users of antibiotics is counted during a full year versus at a specific day in that same year. Since antibiotics are used only for short periods, the number of drug users at a specific day will be markedly lower than the number of users counted during the full year. For drugs with high discontinuation rates, for example, drugs against attention deficit/hyperactivity disorder,[3] use of period prevalence might, for the same reason, lead to misunderstandings or misinterpretations about the total number of drug users. In general, the time period over which the period prevalence is measured should be carefully considered and depend on the type of drug being studied. For drugs used short term such as, for example, antibiotics, a count of the number of dispensed prescriptions in a time period may be a better measure of drug use than the period prevalence.

4 | ADHERENCE TO MEDICATIONS

Adherence is "the process by which patients take their medications as prescribed…"[4] According to the taxonomy proposed by Vrijens et al.,[4] adherence consists of three components: (1) initiation of treatment; (2) implementation of the dosing regimen; and (3) discontinuation or persistence with treatment. Initiation of treatment measures to what extent the patient chooses to start using the medication and can, unlike discontinuation/persistence and implementation, not be measured from drug dispensing data or prescribing data alone. The golden standard to measure initiation is record linkage between medical records data on prescriptions issued and dispensing data from pharmacies. The measurement of treatment adherence is limited to chronic medications or medications prescribed multiple times as the measures presented below requires the filling of multiple prescriptions over a period. Further, as it requires the observation of longitudinal dispensing patterns each individuals' available follow-up time in the database must be considered in the analysis. Various measures can be used to study adherence to medications and efforts have been put into harmonizing these measurements.[5,6] The construct of the specific adherence measure should be adapted to the prescription regulations and reimbursement rules in the individual country. Below, we give an overview of how individual-level drug dispensing data can be used to calculate different measures of treatment persistence and implementation. Of note, implementation and persistence are interlinked as a patient can be persistent with treatment but have suboptimal implementation. This common limitation to research in treatment adherence is further discussed by Caetano et al.[7] Often, it will be relevant to combine measures of persistence and implementation to give a two-dimensional and more complete picture of treatment adherence.

4.1 | Measuring treatment persistence

Treatment persistence is measured as the time from initiation of treatment until discontinuation. Non-persistence is the time from discontinuation and until the end of prescribing.[4] Preferably, treatment persistence should be based on information on the prescribed daily dose and amount of dispensed drug, for example, by using a "days' supply" variable. However, if such a variable is not available, as is the case in many individual-level databases on dispensed drugs, methods used to estimate treatment persistence must rely on strong assumptions of the prescribed daily dose and thus the duration of prescriptions. There are several approaches to estimating the duration of a prescription. One approach is to base the estimation on the number of dispensed tablets or the amount of dispensed DDDs assuming that the prescribed daily dose correlates to 1 tablet, 1 DDD, or the clinically recommended minimum dose. Depending on how well the DDD correlate with the clinical recommended dose, the number of tablets may be preferred over DDDs when estimating prescription durations. This could be relevant for drug utilization studies in children or in specific subpopulations such as the elderly or those with reduced renal function where a dose reduction is recommended. As an illustration of this, Sinnott et al.[8] used US pharmacy claims data to estimate and compare prescription durations based on the assumption of a daily intake of 1 DDD versus recorded data on days' supply. They found that when using the DDDs, the median prescription durations were overestimated for non-steroidal anti-inflammatory drugs, underestimated for atypical antipsychotics, statins, metformin and warfarin, and showed good agreement for proton pump inhibitors, Cox-2 inhibitors and angiotensin converting enzyme (ACE)-inhibitors.[8] In some cases, it is possible to assign each prescription with a fixed duration of

3 months depending on local prescribing guidelines or reimbursement regulations. While it is beyond the scope of this review, more advanced statistical methods, such as the waiting time distribution[9] may also be used to estimate prescription durations.

4.1.1 | Using the anniversary model

The anniversary model is one of the simplest ways to measure treatment persistence[7,10] as no consideration is given to the duration of the single prescription. In the anniversary model, a patient is considered persistent for 1 year if a prescription is refilled during a specific interval surrounding the anniversary of the first prescription.[7] In Figure 1 a hypothetical patient is considered persistent as a prescription is refilled within 3 months of the anniversary of first prescription (fourth prescription is filled at day 300). Specific considerations apply regarding the choice of the interval surrounding the anniversary of treatment initiation and can be found elsewhere.[10]

4.1.2 | Using the refill gap method

The refill-gap method measures persistence based on gaps between prescription refills[10] and is one of the most common measures of treatment persistence when using individual-level drug dispensing data.[11] A patient is considered non-persistent when the gap between prescription refills exceeds the days supplied plus a permissible gap. A grace period is added to allow for late prescription refills in case of suboptimal implementation (see below) or stockpiling. This grace period can be fixed to, for example, 90 days, or relative to the days supplied or estimated prescription duration, for example, 20%, but it should ideally be based on a clinical or pharmacological rationale. In Figure 1, the hypothetical patient would be considered non-persistent after 120 days if using a grace period of 60 days while he would be considered persistent if using a grace period of more than 90 days. Persistence by the refill-gap method is often estimated using a Kaplan–Meier survival curve[11] with the y-axis showing the proportion of persistent patients and x-axis showing the time (Figure 2). Such a curve could, for example, inform that 60% of patients are still treated 180 days after treatment initiation. Patients need to be censored from the analysis when their drug dispensing cannot be assessed. This could either be when they die, when they move out from the country or when they are hospitalized for a longer time and receives medicine in hospital which cannot be identified. It is important to note that the refill-gap method is highly sensitive to assumptions of the prescription duration and the length of the chosen grace period.[11] Per definition, a long grace period allows for a higher degree of suboptimal implementation and irregular prescription refills and will therefore yield a low estimate of the proportion of non-persistent patients.[12] Therefore, to ensure that estimates of persistence are robust, it is advisable to conduct multiple sensitivity analyses with varying lengths of the grace period.

4.1.3 | Using the proportion of patients covered method

The proportion of patients covered (PPC) method estimates the proportion of alive patients that are covered by treatment at a given day after treatment initiation.[13] When a patient is no longer covered by treatment at a given day that patient is excluded from the numerator of the PPC. However, the patient reenters the numerator when refilling a prescription which is an important distinction from the Kaplan–Meier survival curve. Patients need to be removed from both the numerator and denominator when their drug dispensing cannot be assessed, for example, due to death or migration. In the standard approach, the PPC is calculated at each day of the observation period. However, other approaches are possible where the PPC is estimated based on periods.[14] The PPC can be shown in a curve displaying the

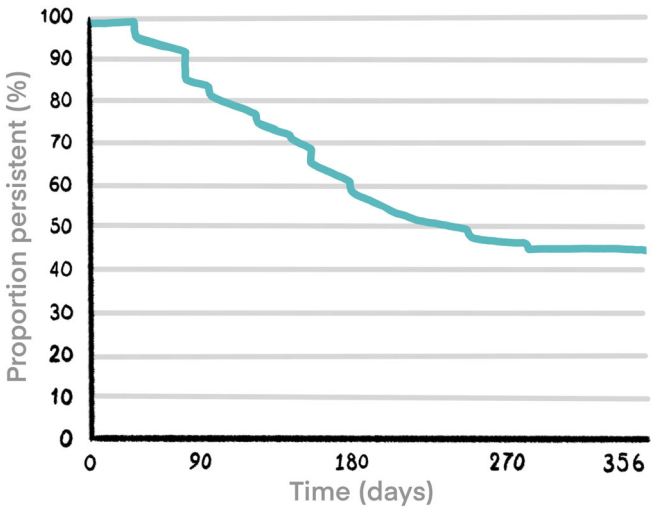

FIGURE 2 A hypothetical example of a Kaplan–Meier survival curve of drug persistence displaying the proportion of persistent patients over time. Along the y-axis is the proportion of persistent patients and along the x-axis is time. After 180 days 60% of patients are still in treatment

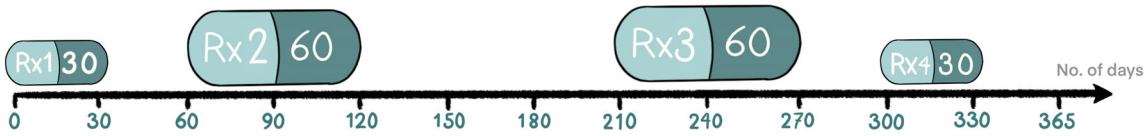

FIGURE 1 Schematic illustration of a patient filling multiple prescriptions (Rx) over a period of 365 days. The number inside the tablets indicate the number of dispensed tablets, for example, 30 tablets are dispensed at day 0

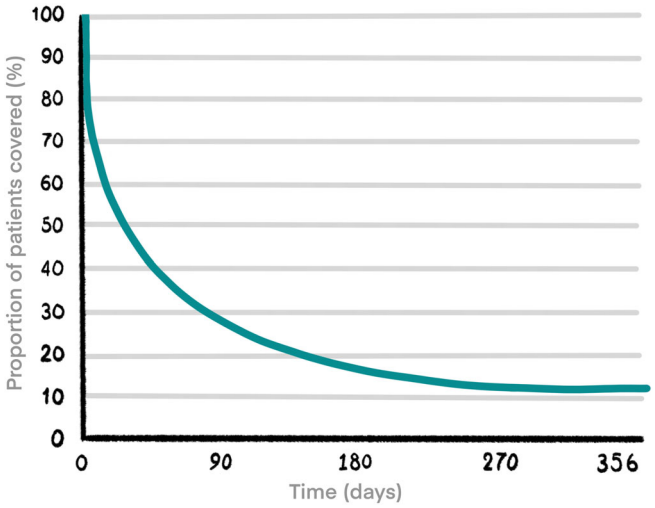

FIGURE 3 A hypothetical example of a curve displaying the proportions of patients covered (PPC) by treatment over time. Along the y-axis is the proportion of patients covered by treatment and along the x-axis is time. At day 90, 30% of patients are covered by treatment

PPC by a prescription along the y-axis and time along the x-axis (Figure 3). Such a curve could, for example, inform that 30% of patients are covered by treatment at day 90 after treatment initiation.

4.2 | Measuring implementation

Implementation refers to "…the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose."[4] As with the measures of treatment persistence, measures of implementation rely on strong assumptions on the prescribed daily dose. There are various ways to describe the implementation of dosing regimens. Two of the most common implementation measures based on drug dispensing data is presented below.

4.2.1 | Using the proportion of days covered

The proportion of days covered (PDC) calculates the proportion of days a patient has medication covered within a fixed interval.[7] The PDC could for example be calculated over a fixed interval of 365 days or 6 months. In Figure 1, a hypothetical patient has medication supplied for 180 days over a period of 365 days yielding a 1-year PDC of 49% (180/365 days) and a 6-month PDC of 50% (90/180 days). There are various operational definitions of the PDC. In other examples, the PDC is calculated over the number of days between the first prescription and the end of the last refill.[15] Most often, the PDC is capped at 100%, thereby truncating oversupply,[6] meaning that excess medication supply due to early refills and prescription overlap is not considered. The PDC may be used as a continuous measure by calculating the PDC for each patient and summarizing the mean PDC in a population.[6] The PDC is often reduced to a categorical measure based on a specific threshold of, for example, 80%, defining whether a patient has suboptimal implementation or not.[7] This threshold as well as the length of the period over which the PDC is calculated should be guided by clinical or pharmacological rationale.

4.2.2 | Using the medication possession ratio

A closely related measure of implementation is the medication possession ratio (MPR) which sums the medication supply within a specific period divided by the days in that period.[5] Normally, the MPR considers excess supply of medication when prescriptions are overlapping due to early refills and it can therefore exceed 100% which is the main difference from the PDC. As with the PDC, there are various operational definitions of the MPR.[16] Good examples can be found in papers by Malo et al.,[15] Baumgartner et al.,[17] and Raebel et al.[6]

4.3 | Combining measures of adherence

As mentioned above, it will often be relevant to combine measures of persistence and implementation. The refill-gap method for example only reflects one aspect of adherence while using the PDC and MPR measures alone does not give information on the time of discontinuation. Measures of adherence could be combined by identifying patients who are persistent with treatment for a given period of time and then calculate the implementation during this period using the PDC or the MPR.[10] As an example, in a Swedish study, the MPR was calculated only among patients who were persistent to non-vitamin K oral anticoagulants.[18]

4.4 | Suggested reading

For further reading on the taxonomy of adherence, we refer to the framework paper by Vrijens et al.[4] For further reading on different measures of adherence, we refer to papers by Caetano et al.[7] and Andrade et al.[16]

5 | DRUG COMBINATIONS AND SWITCHING

Individual-level drug dispensing data may be useful to assess concomitant use of different drugs. Such analyses could focus on polypharmacy, drug–drug interactions (DDIs), or duplicate use. However, it is often difficult to distinguish combination use from switching and the risk of misclassification should be kept in mind.[19]

5.1 | Identifying concomitant drug use

The simplest method to assess concomitant drug use is to count dispensed drugs within a pre-defined observation window (see top of

Figure 4). The choice of this time period should be adapted to the prescription regulations and reimbursement rules of the individual country. In some countries, chronic medication is prescribed for 1 year on each prescription and patients go to pharmacies every third month to fill their prescription. Consequently, an observation period of 3–4 months would rather well mirror concomitant use of different medicines, although it may misclassify switching as combination use if no consideration is given to the sequence of prescriptions (see below). Other countries with other dispensing regulations may have other suitable time-windows. A more exact approach to identify concomitant drug use is to assess the extent of overlapping prescriptions for different medications. This is done by defining an index date and identify prescriptions filled for different drugs (drug A and B) surrounding the index date (see bottom of Figure 4). The extent of overlap is hereafter assessed using the same analyses as described under adherence.

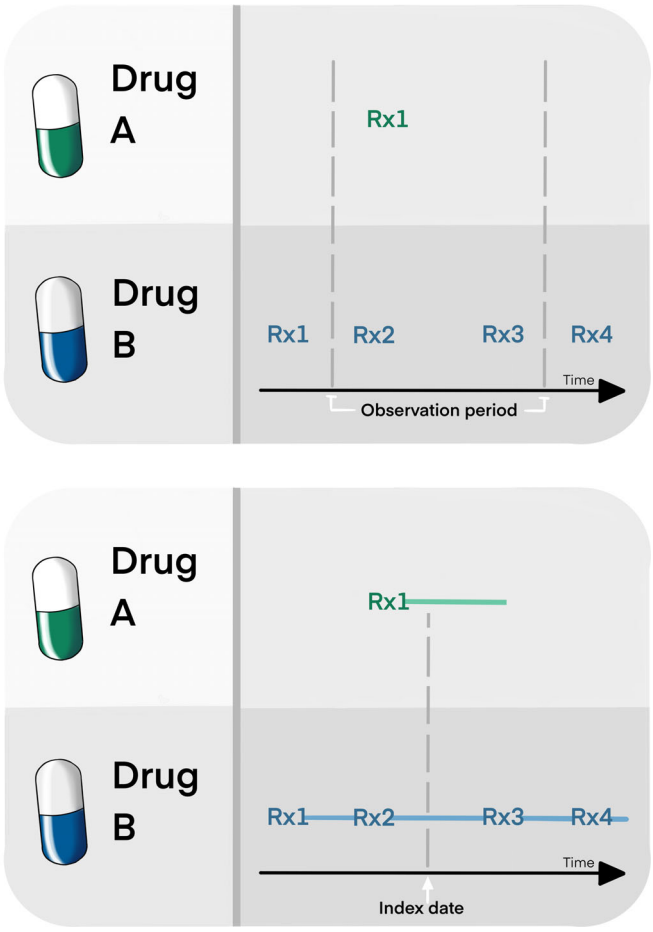

FIGURE 4 Schematic illustration of two alternative ways of identifying concomitant drug use in a hypothetical patient being dispensed drug A and B over a time period. In the top of the figure is an example where concomitant drug use is identified based on dispensed drugs within an observation period. In the bottom is an example where concomitant drug use is assessed based on an index date. Prescriptions for drug A and B surrounding the index date is identified followed by an assessment of the extent of overlapping prescriptions between drug A and B. Rx = dispensed prescriptions. Red/blue lines reflect constructed prescription durations

5.2 | Identifying DDIs

DDIs can occur when two or more drugs are concomitantly administered to a patient.[20] Since clinical outcomes of concomitant prescribing may be difficult to assess, the term "potential DDI" is commonly used in drug utilization studies to describe a combination of drugs that may have harmful consequences for the patient. Potential DDIs can be assessed with individual-level drug dispensing data applying the methods described above, that is, either using dispensed drugs during a pre-defined time window or more detailed assessment of each patient's time under treatment of each drug (Figure 4). None of the methods may, however, be completely accurate. The former method may misclassify switches as combinations and the latter may fail to detect short courses and add-on therapy. However, studies comparing the two methods have found acceptable agreement.[21] For studies of DDIs, drug dispensing data is combined with information from a DDI-classification system such as Swedish Finnish Interaction X-referencing (SFINX),[22] Micromedex[23] and so forth. There are several DDI classification systems used globally, which in combination with differences in study populations may be a reason why the prevalence of potential DDIs differs markedly between studies. Of note, substantial differences and inconsistencies between different DDI-classification systems have been reported.[24,25]

5.3 | Identifying switching

Appropriate assessment of switching requires longitudinal analyses of drug dispensing patterns using the same methods as described under "adherence" above. As for the adherence measure, this means that in databases without continuous enrollment where there is a high turnover of patients, each individual's available follow-up time in the database should be considered. The first step is normally to apply a washout period without any dispensed drugs to identify new users as described under "incidence of drug use" above. This is followed by consecutive analyses of filled prescriptions. A drug switch is then defined as the replacement of a patient's dispensed drug with another drug dispensed. Depending on the aim of the given drug utilization study and the clinical question, switching patterns may focus on switching between different formulations of the same brand, between brands of the same substance (e.g., from original product to a generic alternative) or between two different substances used for the same indication (e.g., therapeutic substitution). The number of drug switches may be expressed as a percentage of the total number of consecutive prescription fillings or as a proportion of all patients undergoing switch. Studies on drug switches over time could simply count the number of different drugs dispensed or assess the sequential order of dispensed drugs over time. Assume as an example a patient that is being dispensed two generic alternatives (drug A & B) over a 1-year period in this sequential way: AAABBB versus ABBAAB. In the first case, there will be one switch, in the latter there will be three, and in both cases the patient has been exposed to two different generics.

5.4 | Identifying polypharmacy

Polypharmacy is most commonly defined as the concomitant use of five or more medications by an individual.[26] However, this definition is still under debate and there are also other definitions, for example, within pediatrics.[27] Sometimes the term "multiple medications" is used in studies assessing all kinds of medicines dispensed during a time-window.[28] The challenge in assessing polypharmacy with individual-level drug dispensing data lies in how to distinguish concomitant use from discontinuation and switches as presented above. The most appropriate assessment of polypharmacy requires assessment of time under treatment and the potential exclusion of topical drugs and certain medicines used for short-term treatment. The refill pattern method is an example of a polypharmacy measure that considers time under treatment[29] and which is able to distinguish between switches and concomitant drug use. There are, however, no uniform definitions of and most studies use the total number of individual drug substances, that is, at the fifth ATC level as a simple measure of polypharmacy.

5.5 | Suggested reading

For further reading on different methods to assess drug combinations, we refer to the papers by Bjerrum et al.[21] and a study on potential DDIs in the entire Swedish population published by Holm et al.[30]

6 | PRESCRIPTION DRUG MISUSE AND SKEWNESS IN DRUG USE

Individual-level drug dispensing data can be used to identify and construct potential indicators of prescription drug misuse such as skewed distributions in the dispensed volume of drug use or the phenomenon of doctor-shopping.

6.1 | Identifying potential prescription drug misuse

Individual-level drug dispensing data are increasingly used to explore prescription drug misuse.[31] A range of different methods and varied thresholds for misuse are being used, but four common proxies for prescription drug misuse have been identified: (1) number of prescribers, that is, doctor-shopping, (2) number of pharmacies dispensing, (3) volume of drug(s) dispensed, and/or (4) overlapping prescriptions/early refills.[31] Doctor-shopping is a simple measure which involves counting the number of different prescribers a patient has received prescriptions from during a specified time. However, no generally accepted definition of doctor-shopping exist and the appropriate cut-offs should be based on the drug and disease studied and the type of source data used in each specific study.[32] As an example, doctor-shopping of opioids has both been defined as (1) the filling of >1 prescription by ≥2 different prescribers with ≥1 day of overlap and filled at ≥3 pharmacies; and (2) the filling of ≥2 prescriptions by different doctors within ≥1 day overlapping in the duration of therapy.[32] As shown with the example, proxies for prescription drug misuse may be used in a combined measure but they can also be used as stand-alone proxies. Furthermore, proxies for prescription drug misuse can be applied on a population-level to identify the proportion of a population involved in suspect prescription fill behavior, the amount of dispensed drug in a population obtained by doctor-shopping,[33] or they can be applied on the level of the individual patient to identify subgroups of potential prescription drug misusers. Specifically for doctor-shopping, it is important to note that it is a complex multi-factor phenomenon which represents a broad range of patient behaviors.[34] The patient rationale for the excessive use of medications through doctor-shopping may vary from clinician-related factors to patient-related factors. Doctor-shopping may simply be related to office factors such as practice formularies not prescribing particular medications at initial consultation, clinician characteristics, communication concerns, and/or patient illness characteristics. In general, it is important to carefully consider how each of the four proxies mentioned above can be used to identify prescription drug use in a given study as this depends on the structure of the health care system and the drug and disease being studied. Lastly, in general it is worth to note that the chosen cut-off used in a proxy to define prescription drug misuse can affect the proportion of patients classified as potential misusers.[35]

6.2 | Identifying skewness in drug use

An inverse Lorenz curve may be used to show the distribution of medication use among the population using the drug. It can reveal if there is skewed distribution of drug volume in the population of drug users.[36] The x-axis represents the percentile of the population using the drug, ranked from those with the lowest medication volume to the highest, while the y-axis represents the percentile of the total drug volume (Figure 5).[37] The curve can be used to read off statistics such as the top 1% of the population uses 40% of the medication. As an example, an inverse Lorenz curve was used to show that 1% of opioid users accounted for 19% of the drug volume suggesting there are some heavy users of opioids in the population.[36] Of note, skewness in drug use may observed for many different reasons, for example, when a drug is being misused resulting in heavy users and sporadic users of a drug (e.g., opioids), or when a drug is used in different dosages and/or in different durations with different indications (e.g., steroids). Parts of those using small amounts may also be patients initiated on the therapy during the year or people deceased during the year.

6.3 | Suggested reading

For a systematic review on proxies of prescription drug misuse, we refer to the review by Blanch et al.[31] For further reading on the

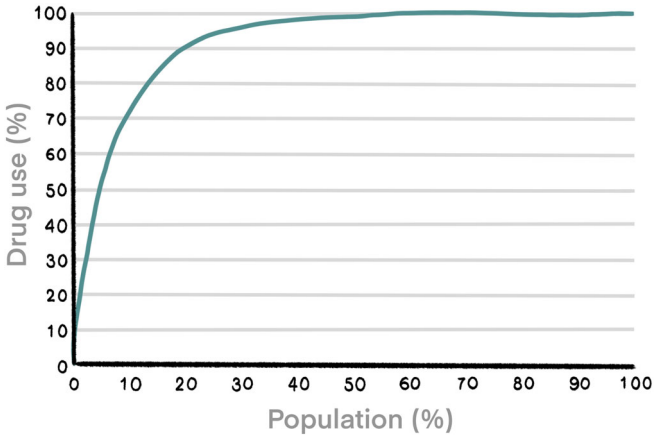

FIGURE 5 A hypothetical example of an inverse Lorenz Curve to assess skewness in drug use in a population of drug users. Along the y-axis is the percentiles cumulated share of the total drug volume and along the x-axis is the percentiles of the population using the drug. Skewness in drug volume is seen when the curve is moved toward the upper left corner reflecting that a small proportion of the population of drug users is responsible for a high proportion of the total drug volume

inverse Lorenz curve and examples, we refer to the paper by Hallas and Støvring.[36]

7 | QUALITY OF MEDICINES USE

Individual-level drug dispensing data can be used to examine quality of medicines use. PQIs and analyses of variation in drug use across different population subgroups, regions, or countries are important tools in improving quality of medicine use.[38,39]

7.1 | Prescribing quality indicators

PQIs are defined as "a measurable element of prescribing performance for which there is evidence or consensus that it can be used to assess quality, and hence in changing the quality of care provided."[40] PQIs are used to assess appropriate prescribing and use of drugs in a population or a practice. They can be divided into drug-oriented, disease-oriented, and patient-oriented PQIs depending on the amount of clinical data they include.[40] Drug-oriented PQIs focus on the drugs and have no information on the diagnoses or conditions for which they have been prescribed. Such indicators can be used to identify important drug-related quality issues including drug duplication, polypharmacy, DDIs and treatment adherence, as described above. If data are available, individual-level drug dispensing data can be linked to other patient-level data containing patient's disease, diagnosis, or health status to give disease-oriented PQIs that will identify the quality of care for a specific disease or condition. For example, linking individual-level drug dispensing data with diagnosis of atrial fibrillation, a disease-oriented PQI would be the proportion of patients with atrial fibrillation receiving anticoagulants. Patient-oriented PQIs contain more in-depth clinical data on patient characteristics and disease history to assess appropriate use in individual patients. An example of a patient-oriented PQI is the proportion of patients with hypertension between age 18 and 80 years with chronic kidney disease in stage 4–5 who are prescribed antihypertensives.[41] It is possible to construct disease- or patient-oriented PQIs using only drug dispensing data as proxies for diagnoses, disease severity and risk factors, but the validity of such indicators needs to be assessed.[42] One example of a disease-oriented PQI based only on individual-level drug dispensing data is the use of inhaled corticosteroids among heavy users of beta-adrenoceptor agonists.[43] Other examples of each type of PQI can be found in the literature.[40] While out of the scope of this review, it is important to note that PQIs may also be developed based on aggregate drug dispensing data. Examples of such indicators are ratios between volumes sold of different drugs.

7.2 | Variations in drug use

Studies of variation in healthcare processes and outcomes are one of the keys to quality improvement.[44] Therefore, analyses of variations in drug utilization are important tools in improving quality of medicine use.[38,39] Some variation in drug utilization is desirable when comparing populations, given that patients differ and should be treated individually. Other variation may indicate lack of clinical consensus or varying suboptimal implementation of established consensus. Comparative analyses of drug utilization may be conducted either focusing on the populations treated or the individual doctors, practices or clinics issuing the prescriptions.[38,39] Population-based comparisons may be conducted on different hierarchical levels from intercontinental, international (cross-national), national to local studies in small regions or districts. Individual-level drug dispensing data can be used in all these studies, either analyzed with epidemiological measures such as prevalence or incidence, or other measures presented in this paper. A common methodology when comparing different geographical areas is Small Health Area analysis including calculations of utilization rates for the drug in each area, descriptive statistics, identification of important differences, and attempts to explain the variation.[38,45] Small areas in healthcare may be regions, municipalities, districts, or post code areas. The normal procedure for Small Health Area analysis is presented in Box 1.

8 | CHARACTERIZING DRUG USERS AND PRESCRIBERS

Depending on data availability and linkage possibilities, drug users can be characterized according to simple demographic variables such as age and sex, sociodemographic variables such as income and education level, and concurrent drug use and/or comorbidities. It will often be relevant to stratify measures of drug use according to age, as age is often an important determinant of drug use. Likewise, differences in disease patterns between males and females may be reflected in

BOX 1 Stepwise approach of Small Health Area Analysis using individual level drug dispensing data

Steps in the analysis

1. Identify and define the geographic boundaries of the areas, for example, districts, municipalities, regions.
2. Estimate the number of individuals being dispensed the drug(s) of interest (numerator).
3. Identify the population living in each area during the same time-window (denominator).
4. Calculate utilization rates—these may be calculated for each area on a crude and age-adjusted basis, usually using the indirect method of standardization.
5. Potentially do further adjustment or stratification to handle case-mix between populations.
6. Analyze the results, normally through one of the two methods below
    - Compare rates between areas of high and low utilization
    - Correlation analyses to establish relationships between utilization patterns and different characteristics

differences in drug use. If data on diagnoses or treatment indications are available, the proportion of a population using a given drug off-label may be described. Here, it is important to distinguish between off-label use "on evidence" and off-label use "off evidence."[46] The first may often be clinically appropriate while the latter might reflect irrational drug use. If data on diagnoses are not available, dispensed drugs can be used as a proxy for comorbidity. Several studies have analyzed how different measures of comorbidity predict health care needs, healthcare consumption, and mortality.[47] A study showed that the number of prescribed drugs was a powerful measure for predicting future consultations and mortality.[48] A challenge in using the number of drugs as a measure of comorbidity is that the definition of "drug" can vary between studies and that there is a large variation between countries in how healthcare is organized and the completeness of data.[47] Besides the number of drugs, dispensed drugs may also be used as a marker of a specific disease,[49] for example, dispensed prescriptions for diabetes medication as a marker of diabetes.

In addition to the description of drug users, another important and often overseen aspect in drug utilization studies is the description of who prescribes the drug.[50] Not all databases on dispensed drugs contain this information. However, when available, detailed knowledge from drug utilization studies on who is responsible for initiating and maintaining drug treatment can be central to target new interventions and guidelines. Knowledge on who prescribes drugs may also be valuable as part of the quality assessment of whether treatment guidelines are being adhered to. Of note, the organization of health care systems varies widely between countries which will be reflected in the assessment of who prescribes drugs.

9 | CLOSING REMARKS

Drug utilization studies are essential to facilitate rational drug use. By using the measures presented above, drug utilization studies can identify or raise awareness of problematic or unexpected patterns of drug use which may then lead to risk minimization measures. Problematic or unexpected patterns of drug use may be reflected in: (1) an increase or decrease in the incidence or prevalence of a drug comparing year on year use in a population; (2) low levels of treatment adherence; (3) unexpected patterns of drug combinations or switching; (4) patterns indicative of prescription drug misuse or skewness in drug use which cannot be explained by other patient-related or drug-related factors; (5) characteristics of drug users which could imply off-label use or contraindicated use, or the distribution of drug prescribing between different prescriber types; or (6) PQIs or unexpected variations in drug use between populations, practices or countries. The methods described in this review provide a comprehensive, yet not exhaustive, list of potential analytical approaches, which we hope will serve as an inspiration for future drug utilization studies.

ACKNOWLEDGMENTS

The authors would like to thank Jesper Hallas and Emma Bjørk for valuable input to the final version of the manuscript and Sissel Mogensen for help with figures.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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How to cite this article: Rasmussen L, Wettermark B, Steinke D, Pottegård A. Core concepts in pharmacoepidemiology: Measures of drug utilization based on individual-level drug dispensing data. *Pharmacoepidemiol Drug Saf*. 2022;31(10):1015-1026. doi:10.1002/pds.5490