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CHAPTER 3.5.3

Assessment of medication adherence in databases

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KEY POINTS

- Prescription and dispensing data can be used for assessing adherence to medication in a defined population.
- Medication adherence researchers are strongly recommended to provide a good description of the adherence construct being measured, the measurement being used (including any treatment reference time window or any permissible gap period), and the results of their sensitivity analyses.
- If used judiciously, electronic healthcare data can provide adequate measures of drug treatment initiation, adherence, and persistence.

Key words

Medication adherence, electronic databases, prescription data, dispensing data

Introduction

In a report published by the World Health Organization (WHO) in 2003, adherence is defined as "*the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a health care provider*" (1). The term medication adherence, more specifically, has been defined as "*the process by which patients take their medication in correspondence with health care provider recommendations*". Based on the Ascertaining Barriers to Compliance (ABC) taxonomy, medication adherence is composed of three parts: initiation, implementation, and discontinuation (2), as defined in chapter 3.4.1.

Adherence to drug treatment can be assessed in several contexts and for different purposes. In clinical trials and comparative effectiveness and safety studies, medication adherence is generally measured to provide an estimate of the intensity of drug exposure (see e.g. (3)). In the context of routine clinical practice, it is of special interest to understand how patients take their drugs, identify the determinants of those behaviours, and develop and test interventions to optimize medication use, in order to ensure optimal treatment outcomes. This chapter focuses on methods for the assessment of medication adherence using electronic databases, presenting a summary of topics crucial in this context including aspects of study design, measurements of adherence, and issues specific to the use of electronic health records. Furthermore, this chapter provides an overview of the strengths and limitations of database research for adherence assessment; and highlights existing guidelines for the reporting of database studies.

General methodological considerations

Assessing medication adherence using electronic health records is not dissimilar to using purposely collected data, as described in chapter 3.5.2. However, due to differences in the available data, certain questions lend themselves to database research rather than field research – and vice versa. Most importantly, since data is usually collected for purposes other than research in clinical practice (e.g., reimbursement of healthcare providers or healthcare statistics), database research requires thorough planning, design, and reporting of studies to account for the lack of potentially relevant contextual information. For

instance, indication for prescriptions is not always available in databases used for medication adherence research, as is any information with regards to if/why medication might have been stopped. Similarly, databases do not contain any patient-reported data, such as details around how/how often (or when) they, in fact, take their medication. Nevertheless, electronic health records are usually available for large populations, and cover considerable time periods; making results more generalisable than small-scale field research projects – albeit only within the (possible) constrains of their scope and coverage.

Data sources available: Prescribed versus dispensed data

To provide an in-depth, useful, and reliable description of patients' adherence to medication, both prescription and dispensing data as obtained from electronic health records, registries, or administrative databases are needed. Keeping in mind the definition of medication adherence, prescription data is required to enable assessing the extent to which a patient takes their medication according to a pre-agreed therapeutic plan with the prescriber/healthcare provider; in contrast, dispensing data is required to facilitate the evaluation of patients' drug possession, i.e., whether they indeed have access to the correct medication, in sufficient quantities. Unfortunately, electronic databases comprising information on both prescription and dispensing data are rare and, in this context, it is key to understand the information that is available when using exclusively dispensing or prescription data to appropriately interpret medication adherence estimates (or proxies thereof).

Well known electronic databases, such as the Clinical Practice Research Datalink (CPRD) in England (4), contain prescription-only information from primary care. These data can offer insights into prescribing behaviours or physicians' adherence to guidelines; however, they do not constitute a valid data source for medication adherence assessment, not knowing if the patients are filling their prescriptions at the pharmacy. If no other data source is available, prescribing-only data may be used as a proxy of drug exposure.

Dispensing data, such as those included in the Scottish Prescribing Information System (PIS) (5) or the French national health insurance database (SNIIRAM) (6), provide information on prescribed drugs in a patient's possession. If the research focus is on quality of prescribing,

dispensing data are less informative than prescription data since an unknown proportion of prescriptions may have been issued but not filled by patients. In the context of medication adherence specifically, dispensing-only data do not capture patients who do not fill any prescription; consequently, these data do not allow the assessment of primary medication non-adherence, i.e., instances where a new drug is prescribed but the patient does not obtain it in the first place. Nevertheless, dispensing data are useful for measuring secondary medication adherence (i.e., adherence to medication after a patient has initiated treatment) if the administrative database provides information on number of days supplied or facilitates calculation thereof, for example by providing a complete record of all dispensations including dates and drug quantities dispensed. Similar to prescribing data, dispensing data have their limitations; most importantly, researchers need to be aware of any rules that apply to the administrative data they intend to use to measure adherence, e.g., the specific populations covered by the dataset; the included drug range; or any other relevant rules regarding dispensing and/or the renewal of prescriptions, which may vary by jurisdiction.

Electronic health records such as the Valencia Health System Integrated Database (VID) in Spain (7) or linked datasets in Brazil (8), where both prescribing and dispensing information are available, can provide the most reliable and accurate information on medication adherence (9). First, it is possible to accurately define the initiation or index date, which is the moment when the prescriber starts/initiates the treatment (date of first prescription), information that can be considered in the implementation or secondary adherence phase. Second, it also enables the assessment of primary adherence and allows the inclusion of fully non-adherent patient in any further analyses, i.e., those who did not fill any prescription in the assessment period after the treatment was initiated. And, finally, the linkage of prescription and dispensing information allows to censor periods without prescriptions, which would otherwise be considered as gaps in days' supply, and thus incorrectly defined as periods of non-adherence.

Study design

The most appropriate study design for any adherence study depends not only on the data sources available for analyses, but also on the topic area, the research question, and the

specific study objectives. Regardless, a universally crucial aspect to consider is the identification of a suitable study cohort and patient eligibility for inclusion in this cohort. Most commonly, drug utilization studies employ a new-user (incident user) design.

Defining what is a new, or incident, user can be challenging using databases. The best approach is to look back through prescribing and/or dispensing records to check whether a prescription for the drug of interest was filled within a pre-specified time period prior to study start, with the aim to correctly identify a patient's index date (date of first prescription). The appropriate length of this look-back (or washout) period depends on the study objective, the population and the target drugs, and potentially other contextual factors (e.g., legal requirement). For example, if the research objective is to assess "initiation of a new major opioid treatment", one might want to consider new episodes of treatment, irrespective of prior treatments; in this case, a short washout period – such as, e.g., three months – might be considered acceptable to define the prescription as being for a new treatment episode. On the other hand, the concept of new episodes may not apply for the treatment of chronic diseases such as hypertension, diabetes, or dyslipidemia; in these cases, the considered look-back period may be longer. In dynamic cohorts, a fixed-cohort period of one to two years is commonly used for chronic medications to ensure that all patients – regardless of the date of first prescription – have the same probability of being treatment naïve at the start of their individual follow-up time. Determining a relevant look-back period also depends on the characteristics of the data source. In some drug plans, prescriptions are dispensed for 30-day periods, while in others they are dispensed for longer (90 days or more). This type of administrative rule should be taken into consideration.

Days' supply estimation

The estimation of days' supply is one of the most relevant aspects when assessing adherence. It can be calculated using the dosage information instructions given by the prescriber if available, by dividing the number of pills contained in each package by the number of pills per day as indicated (e.g., 1 pill of dabigatran 110 mg every 12h, given that the package contains 60 tablets, will be estimated as 30 days' supply). There are alternative approaches that may provide a proxy of days' supply when the dose regime is not available, such as using standard practice estimates (e.g. daily defined dose, DDD (10)) or standard

dosing as recommended in relevant clinical treatment guidelines, although these may produce unprecise/unreliable results. Most importantly, DDDs relate to a drug's main indication in adults and are an expression of average maintenance doses, which may lead to either over- or underestimation of the quantities to be taken per day and, consequently, to a miscalculation of days' supply. Similarly, treatment guidelines are rarely compulsory, and prescribers usually have some degree of choice regarding drug dosages, i.e., this may also lead to either over- or underestimation of days' supply depending on assumptions made (e.g., with regards to indication for prescribing).

In routine clinical practice, it is not uncommon to find overlapping prescriptions or dispensations for different reasons. Some of these may be appropriate, such as a patient filling the medication a bit earlier than expected (considering the days' supply of the previous refill) or losing a package and receiving a replacement prescription by their physician; and others may be inappropriate, such as obtaining additional prescriptions and accumulating medication at home. It is of relevance to explain carefully how these situations were handled when estimating days' supply in a project. For example, if, per design, excess of medication (stockpiling) is allowed, this excess of days' supply would be moved forward to fill possible later gaps until a maximum allowed.

Study periods

Time frames considered in medication adherence assessment have to be carefully defined and described. Once the initiation of treatment is determined, usually as the first prescription or dispensing (depending on the data source available), the look-back periods, to define new/incident vs. prevalent use and baseline covariates, and the assessment period, to estimate medication adherence, should be specified. The election of the duration of these periods would depend on the purpose and objectives of the study; and the disease and the drug class studied. For comparison purposes, a fixed assessment period for all patients should be selected, although information for the whole follow-up may also be provided. The end of the assessment period is commonly set at this prespecified fixed time (e.g., 12 months), unless censoring for any reason occurs. Reasonable causes for censoring may be death, exclusion from insurance/disenrollment, or losses to follow-up (e.g., patients leaving the region/country). Appropriateness of censoring based on medication use

depends on the question and the level of measurement, such as specific drug versus drug class or therapeutic group; in some contexts, censoring patients when a switch or a discontinuation occurs might lead to an overestimation of medication adherence. Additionally, if prescription information is also available, one may censor periods without prescriptions available or censor the assessment period if the physician discontinues the treatment.

An overview of the most relevant concepts in the context of assessing adherence in database research is provided in Table 1.

Table 1: Definitions of relevant concepts

Concept	**Definition**
Initiation (primary adherence)	Filling the first prescription of a new treatment for incident users
Implementation (secondary adherence)	Ongoing process by which the patient fills dispensations as prescribed during a defined assessment period.
Discontinuation	Gap in days' supply (prescriptions) of a certain medication or medication class.
Persistence	Time between treatment initiation and a predefined allowable gap in days' supply/dispensation; can be summarised (binary, persistent yes/no)
Look-back (washout) period	Time preceding the initiation or index date used to define previous exposure of medication and commonly the baseline characteristics of the population studied.
Follow-up/assessment period	Length of time/time period in which adherence is assessed/estimated (e.g., 12-month fixed observation window or whole observation window, if no censoring exists)
Censoring	Date when assessment/follow-up of the patient stops/ends. Commonly defined as end of study, disenrollment, or death.
Days' supply	Days covered by medication filled at the pharmacy.
Stockpiling	Accumulation of medication at home. This term is used when an excess of day's supply exists in a certain period of time.

Measuring medication adherence using databases

There are multiple phases of medication adherence to be measured (initiation, implementation, and discontinuation) to provide a comprehensive adherence picture. Thus, the best scenario would be to assess a patient's medication adherence during the different

phases. This would not always be possible, and in such cases the reasons for not including information on all types of measures should be specified. It is also a key aspect to precisely define the different measures of medication adherence to be estimated/assessed, independently of the terminology used.

Initiation (primary adherence)

Initiation or primary adherence is defined as filling the first prescription of a new treatment in incident users; e.g., the first time a patient with newly diagnosed hypertension is prescribed an anti-hypertensive drug. To measure initiation, information on both prescribing and dispensing would be needed; if only dispensing data is available, primary adherence cannot be assessed since information about medication that has been prescribed but not dispensed is, by definition, excluded from the data. Operatively, an acceptable period of time after the first prescription is allowed to identify a dispensing. The ideal scenario to measure initiation would be to have prescription and dispensing linked by a unique identifier to accurately ascertain if the first prescription was actually filled.

Implementation (secondary adherence)

Once a treatment has been initiated, medication adherence can be measured using databases. This ongoing process, widely called implementation or secondary adherence, assesses mainly medication possession or availability during a defined period of observation.

There are several key aspects to consider when estimating implementation, such as the definition of the period under assessment (denominator), the period covered by medication dispensed or days' supply (numerator), the moment when the assessment starts (initiation or index date), and the moment when the assessment finishes/ends (censoring); this requires information on the medication prescribed, the number of pills per package, and the dosing regimen as defined by the prescriber (or alternatively the days' supply) to be available. These key aspects may be defined differently depending on the data sources used (Table 2), and a clear understanding of them is necessary to interpret and compare medication adherence estimates among studies.

Table 2: Key aspects of assessing medication adherence

Data available	**Start of assessment period (index date)**	**Study period under assessment (denominator)**	**Period covered by medication (numerator)**	**End of assessment period (censoring)**
Dispensing only	Date of first dispensation (not necessarily the first prescription issued/ treatment initiation by prescriber)	• Fixed-time interval: fixed period of assessment (e.g., 12, 24, 48 months) • Last-refill interval: period of assessment until last dispensing or at the time of exhaustion of the last days' supply	Period of time covered with dispensations (days' supply) within the assessment period (denominator)	• Fixed-time interval: death, disenrollment, end of assessment period. • Last-refill interval: last dispensing (or when last dispensing is exhausted), death, disenrollment, end of assessment period.
Prescribing & Dispensing	Date when the physician initiates the treatment (first prescription issued)	Period of time covered with prescriptions (any gaps in prescription are censored for the calculation)	Period of time covered with dispensations (days' supply)	Death, disenrollment, end of assessment period. Gaps in prescription are censored.

There is a wide range of metrics being used to ascertain medication possession, most based on days' supply and other (less frequent) based on medication gaps; the most frequently used metrics are the percentage of days covered (PDC) and the Medication Possession Ratio (MPR) (11). As an example, the most common and ideal way of estimating PDC would be to divide the total number of days covered with medication dispensed (days' supply) in the assessment period by the number of days in a patient's assessment period. If stockpiling is allowed the excess of days' supply would be moved forward to fill possible gaps until a pre-defined maximum (prior gaps in days' supply should not be backfilled). Example calculations of PDC using dispensing and/or prescribing data are presented in Figure 1.

Other more complex methods to assess implementation/secondary adherence exist, such as group-based trajectory models (GBTMs). These models are based on PDC and account for

the dynamic nature of adherence, allowing the estimation of adherence over time among patient cohorts (12). GBTMs are, most commonly, being used to identify different poor adherence behaviours to design and target adherence improvement interventions (13).

Persistence/discontinuation

Persistence is the term generally used to describe the time between treatment initiation and discontinuation, where discontinuation is commonly defined when a predefined period of time without medication available appears. This allowable gap will depend on many aspects such as the disease being studied, the pharmacokinetics of the medication, dispensed number of days' supply, etc. When using dispensation only information, it is not possible to determine whether the discontinuation was prescriber-initiated or patient-initiated. Only when using both prescribing and dispensing information, it is possible to differentiate patient discontinuation of therapy from physician interruption.

When assessing persistence, the most common approach is to estimate time from initiation to a first discontinuation using Kaplan-Meier survival curves. The date of discontinuation is defined as the last day with medication available before the gap in days' supply. In this case, the time frame of assessment can be the whole follow-up (the most informative option) or a fixed time window (e.g., 12 months, 24 months, 48 months). With this approach it is also common to report the percentage of patients who discontinued or were non-persistent, meaning that they exceeded the permissible gap with medication available at least once during the assessment period. This approach is frequently called the refill-gap method (14).

Another approach is to assess the percentage of patients that are still on treatment at a given point in time (e.g., at 12, 24, 48 months after treatment initiation). In this case, patients may have discontinued their medication during a certain period of time prior to the time point used for assessing persistence but have re-initiated and are on treatment at that date. This approach is called the treatment anniversary method (14). Both approaches can be combined for a better understanding of the persistence process, and information on re-initiations or interruptions added.

Examples of persistence estimations are represented in Figures 2 and 3. Figure 2 presents two example calculations based on the refill-gap and anniversary method, respectively; Figure 3 shows the Kaplan-Meier curve of the refill-gap example from Figure 2.

Sensitivity analyses

Considering the range of assumptions that need to be made when assessing medication adherence – for example, with regards to indication for prescribing and daily dose/supply dispensed – it is vital to test these assumptions by conducting sensitivity analyses; i.e. rerun analyses while changing relevant underlying parameters such as permissible gaps or days' supply (15,16). This applies to all stages of adherence (implementation, persistence, discontinuation).

Further aspects to be considered when assessing medication adherence using databases

A number of other aspects need to be kept in mind when conducting drug adherence research using databases, mostly related to the lack of context provided in the available data. Most importantly, as previously alluded to, *not having an indication for drug use may have implications on the accuracy of findings*; many drugs are being used for the treatment of different conditions but using diverging dosing schemes and/or different treatment durations. For instance, oral anticoagulants are frequently used to prevent strokes in patients with atrial fibrillation, requiring life-long treatment; in contrast, patients who experienced a deep vein thrombosis will generally be treated for a fixed time period of six months – i.e., these patients may incorrectly be flagged as having discontinued treatment (being non-persistent) if only dispensing data, without indication for treatment, were available. Furthermore, the majority of drug classes contain more than one individual drug, with patients potentially being changed from one to the other for various reasons. To stick with the example of oral anticoagulants, patients might be switched from warfarin to one of the newer, direct oral anticoagulants to reduce the number of healthcare contacts (no regular INR testing is required for direct oral anticoagulants); depending on the level of detail present in the database and the method of analysis, this switch may be defined as a discontinuation, with a patient being categorised as non-persistent to the *drug* in question

although the patient could be considered to be persistent to the *drug class*. Similarly, patients may be switched between different drug classes while still being treated for the same condition (e.g., from an angiotensin receptor blocker to a diuretic in hypertension), resulting in what could be interpreted as discontinuation of the *drug / drug class* but would be considered persistent with the prescribed *treatment.*

Additional thought when planning, designing, and conducting medication adherence studies using databases is also required when attempting to address issues such as concurrent adherence – that is, assessing medication adherence to several drugs used simultaneously, either as part of a multi-drug treatment strategy (e.g., ramipril & amlodipine for hypertension) or for the management of different, co-morbid conditions (e.g., metformin and ramipril for a patient with type 2 diabetes mellitus and hypertension). Although adherence to different drugs can be calculated separately it may, from a clinical point of view, sometimes be more appropriate to take a holistic view and assess several drugs in conjunction in order to obtain a fair impression of medication adherence as related to a particular condition. Specifics rely on data availability, and consultation with clinicians may be required prior to study conduct; it may be useful to consider applying methods that have explicitly been developed to calculate adherence to polypharmacy (17).

Another aspect to be considered when assessing medication adherence is the potential presence of “unobservable” periods of time. For instance, in many settings in-hospital episodes are not captured in the available datasets which may lead to inaccurate calculations based on erroneous assumptions (e.g., prevalent medication being dispensed through the hospital pharmacy thus leading to a delay in refilling prescriptions, which may incorrectly be interpreted as a patient being non-adherent) (18). Depending on data coverage, gaps in the data may also occur when patients go on holidays for extended periods of time (which may or may not result in prior stockpiling) or live in more than one country/administrative region, for example work-related. While not being an exhaustive list, some of these issues may help explain the presence of temporary treatment discontinuations, i.e., patients stopping and restarting treatment with a particular drug; it may, however, be prudent to consider alternative reasons for observed medication adherence patterns within a study.

Presentation of findings

Considering the wide range of topics subsumed under the umbrella of medication adherence research and the diversity of available outcome measurements – not to mention the variability in terminology and definitions applied – adhering to best research practice is vital. This includes not only the preparation of study protocols and statistical/data analyses plans, but also the provisioning of detailed descriptions of the methods used, and clear presentations of study findings. Consequently, it is strongly advised to follow appropriate reporting guidelines when drafting manuscripts for publication to facilitate interpretation of results and avoid misunderstandings. Amongst the various guidelines that have been published thus far, the Reporting of Studies Conducted using Observational Routinely-collected Data for pharmacoepidemiology (RECORD-PE) (19) and the ESPACOMP (International Society for Medication Adherence) Medication Adherence Reporting guideline (EMERGE) (20) are potentially the most relevant; a good starting point to identify additional guidelines on methodological standards or to find further information on medication adherence research are the websites of ESPACOMP (21) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (22), respectively. Guidance on topics such as the graphical representation of a study design, which can be a very powerful tool to describe complex studies, are also available (e.g., (23,24)).

Strengths and limitations of database research

The ultimate goal of medication adherence research is to develop and propose efficient means of helping prescribers and patients to better manage drug treatments so that they obtain optimal health outcomes. Adequate measurement is a prerequisite for the development of sound interventions.

Electronic databases offer unprecedented opportunities to conduct drug utilisation studies – including those focusing on patients' adherence to medication – on a large scale, especially if databases are available on a national level. Since data are automatically captured in routine clinical practice usually for clinical, payment, and/or planning purposes, common issues with respect to medication adherence studies such as recall bias are mostly absent.

The range of data most commonly available in electronic databases enables the calculation of a variety of possible measurements, thereby providing the opportunity to present a more insightful picture of patients' drug taking behaviour. Moreover, depending on how data are collected and managed, there may be potential to link prescribing and/or dispensing data with other datasets, enabling the provision of further context. Lastly, software to support the analysis of large datasets to assess medication adherence is now readily available (e.g., the AdhereR package for use with R).

Nevertheless, measuring medication adherence using databases also has some limitations. Most importantly, the underlying assumption is that a prescribed/dispensed drug will, indeed, be taken; however, any pharmacists conducting medication home reviews have seen patients stockpiling filled prescriptions without, in fact, taking the drug. If this occurs, study results represent an overestimation of medication adherence. Nevertheless, several studies have shown a high correlation/consistency between dispensation and patient consumption (25,26). Second, not all drugs a patient has received may be captured within the databases. For instance, drug samples given by physicians to patients are generally not recorded; the same applies to medication paid for privately or bought over-the-counter without a prescription (e.g., low-dose aspirin). This can lead to an underestimation of medication adherence as not all drugs obtained by a patient will have been captured. And lastly, the data themselves may have inherent limitations, particularly with regards to data quality. Furthermore, accessing data stemming from administrative systems may be a complex and time-consuming process depending on local infrastructure and information governance processes.

Table 3: Strengths and limitations of databases in medication adherence research

Strengths	**Limitations**
• Large samples • No recall or desirability bias • Variety of possible measurements supported • Potential to link with other datasets to enrich the data and provide context	• Assumptions (drug possession) • Data availability and accessibility • Data content and capture (e.g., exclusion of OTC drugs) • Data quality (e.g., coverage, missing-ness, coding standards)

References

1. World Health Organization. Adherence to long-term therapies: evidence for action [Internet]. World Health Organization; 2003 [cited 2023 May 26]. Available from: https://apps.who.int/iris/handle/10665/42682

2. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012 May;73(5):691–705.

3. Lauffenburger J, Acri T, Gross R. Studies of Medication Adherence. In: Pharmacoepidemiology [Internet]. John Wiley & Sons, Ltd; 2019 [cited 2023 May 26]. p. 991–1009. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781119413431.ch38

4. Medicines and Healthcare Products Regulatory Agency. Clinical Practice Research Datalink | CPRD [Internet]. 2023 [cited 2023 May 26]. Available from: https://www.cprd.com/node/120

5. Alvarez-Madrazo S, McTaggart S, Nangle C, Nicholson E, Bennie M. Data Resource Profile: The Scottish National Prescribing Information System (PIS). International Journal of Epidemiology. 2016 Jun 1;45(3):714–715f.

6. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiology and Drug Safety. 2017;26(8):954–62.

7. García-Sempere A, Orrico-Sánchez A, Muñoz-Quiles C, Hurtado I, Peiró S, Sanfélix-Gimeno G, et al. Data Resource Profile: The Valencia Health System Integrated Database (VID). Int J Epidemiol. 2020 Jun 1;49(3):740–741e.

8. Guerra Junior AA, Acurcio FA, Reis A, Santos N, Ávila J, Dias LV, et al. Building the National Database of Health Centred on the Individual: Administrative and Epidemiological Record Linkage - Brazil, 2000-2015. International Journal of Population Data Science [Internet]. 2018 Nov 14 [cited 2023 May 26];3(1). Available from: https://ijpds.org/article/view/446

9. García-Sempere A, Hurtado I, Sanfélix-Genovés J, Rodríguez-Bernal C, Peiró S, Sanfélix-Gimeno G. Improving the accuracy of medication adherence measures using linked prescription and dispensation data: findings from the ESOSVAL cohort of patients treated with osteoporosis drugs. Current Medical Research and Opinion. 2019 Sep 2;35(9):1535–44.

10. World Health Organisation. Defined Daily Dose (DDD) [Internet]. 2023 [cited 2023 May 26]. Available from: https://www.who.int/tools/atc-ddd-toolkit/about-ddd

11. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother. 2006;40(7–8):1280–8.

12. Franklin JM, Shrank WH, Pakes J, Sanfélix-Gimeno G, Matlin OS, Brennan TA, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. Med Care. 2013 Sep;51(9):789–96.

13. Dillon P, Stewart D, Smith SM, Gallagher P, Cousins G. Group-Based Trajectory Models: Assessing Adherence to Antihypertensive Medication in Older Adults in a Community Pharmacy Setting. Clin Pharmacol Ther. 2018 Jun;103(6):1052–60.

14. Grégoire JP, Moisan J. Assessment of adherence to drug treatment in database research. In: Drug Utilization Research [Internet]. John Wiley & Sons, Ltd; 2016 [cited 2023 May 26]. p. 369–80. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118949740.ch36

15. Mueller T, Alvarez-Madrazo S, Robertson C, Bennie M. Use of direct oral anticoagulants in patients with atrial fibrillation in Scotland: Applying a coherent framework to drug utilisation studies. Pharmacoepidemiol Drug Saf. 2017 Nov;26(11):1378–86.

16. Choo E, Jung M, Shin J, Lee S. Comparing the Sensitivities of Measures of Adherence to Antihypertensive Drugs Using Korean National Health Insurance Claims Data. Patient Prefer Adherence. 2021;15:1717–28.

17. Arnet I, Abraham I, Messerli M, Hersberger KE. A method for calculating adherence to polypharmacy from dispensing data records. Int J Clin Pharm. 2014 Feb 1;36(1):192–201.

18. Dong YH, Choudhry NK, Krumme A, Lee MP, Wu LC, Lai MS, et al. Impact of hospitalization on medication adherence estimation in claims data. J Clin Pharm Ther. 2017 Jun;42(3):318–28.

19. Langan SM, Schmidt SA, Wing K, Ehrenstein V, Nicholls SG, Filion KB, et al. The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE). BMJ. 2018 Nov 14;363:k3532.

20. De Geest S, Zullig LL, Dunbar-Jacob J, Helmy R, Hughes DA, Wilson IB, et al. ESPACOMP Medication Adherence Reporting Guideline (EMERGE). Ann Intern Med. 2018 Jul 3;169(1):30–5.

21. ESPACOMP. International Society for Medication Adherence [Internet]. Espacomp. 2020 [cited 2023 May 26]. Available from: https://www.espacomp.eu/

22. European Medicines Agency. ENCePP - European Network of Centres for Pharmacoepidemiology and Pharmacovigilance [Internet]. 2023 [cited 2023 May 26]. Available from: https://www.encepp.eu/

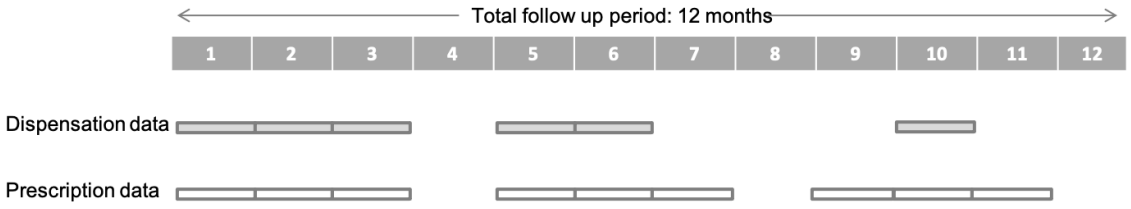
23. Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019 Mar 19;170(6):398–406.

24. Wang SV, Schneeweiss S. A Framework for Visualizing Study Designs and Data Observability in Electronic Health Record Data. Clin Epidemiol. 2022 Apr 29;14:601–8.

25. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: Methods, validity, and applications. Journal of Clinical Epidemiology. 1997 Jan 1;50(1):105–16.

26. Grymonpre R, Cheang M, Fraser M, Metge C, Sitar DS. Validity of a Prescription Claims Database to Estimate Medication Adherence in Older Persons. Medical Care. 2006;44(5):471–7.

Figure 1: Calculation of adherence using Proportion of Days Covered (PDC)



In this example, every prescription and dispensation covers 30 days of medication.

Data sources	Specifications	Days' supply (numerator)	Assessment period (denominator)	PDC
Dispensation only data	Fixed interval	180	360 (whole follow-up period)	50.0%
Dispensation only data	Last-refill interval	180	300 (last refill in month 10)	60.0%
Prescription and dispensation data*	Censoring any period without prescription	180	270 (period covered with prescription without prescription gaps)	66.7%

**When working with prescription and dispensation data, numerator is calculated with dispensation data, and denominator is calculated with prescription data.*

PDC – Proportion of Days Covered

Figure adapted from (9)

Figure 2: Calculation of persistence using the refill-gap and anniversary method

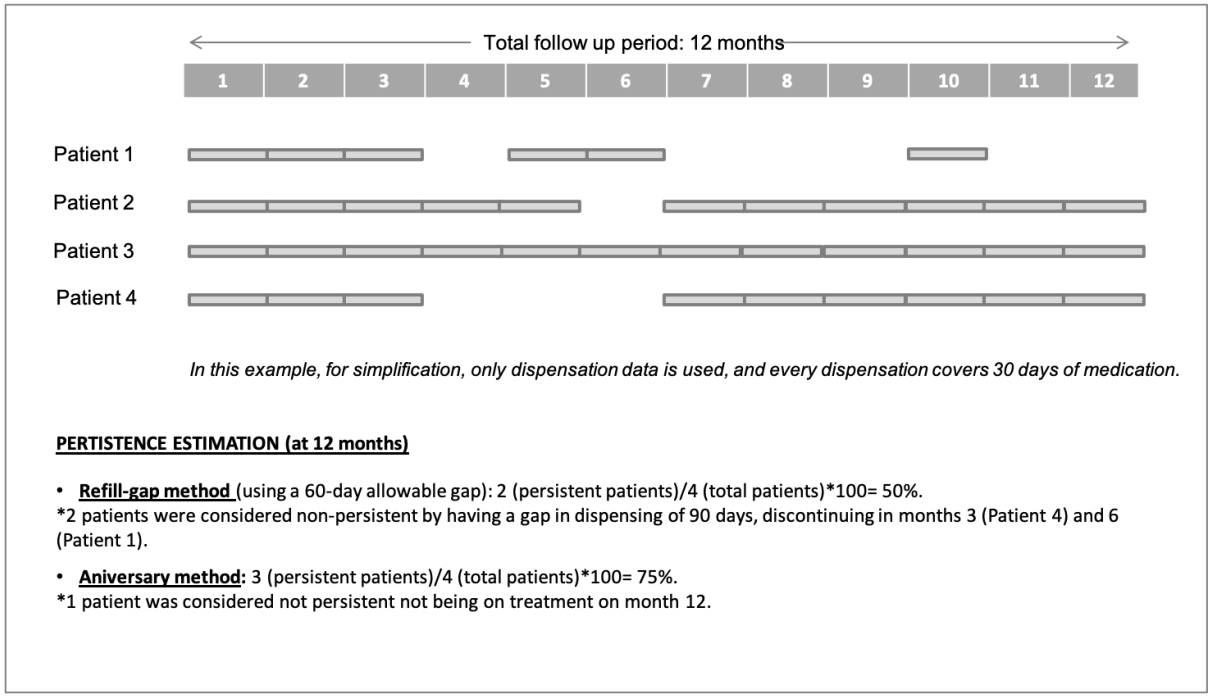


Figure 3: Kaplan-Meier curve of persistence (refill-gap method)