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REVIEW ARTICLE

# Assessing medication adherence: options to consider

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**Abstract** *Background* Adherence to chronic therapy is a key determinant of patient health outcomes in chronic disease. However, only about 50 % of patients adhere to chronic therapy. One of the challenges in promoting adherence is having an accurate understanding of adherence rates and the factors that contribute to non-adherence. There are many measures available to assess patient medication adherence. *Aim of the review* This review aims to present the commonly used indirect methods available for measuring medication adherence in routine healthcare and research studies. *Method* A literature review on medication adherence measures in patient populations with chronic conditions taking chronic medications was conducted through Medline (2003–2013). A complementary manual search of references cited in the retrieved studies was performed in order to identify any additional studies. *Results* Of the 238 initial Medline search results, 57 full texts were retrieved. Forty-seven articles were included as a result of the manual search. Adherence measures identified were: self-report (reported in 50 publications), electronic measures (33), pharmacy refills and claims data (26) and pill counts (25). Patient self-report, electronic measures, pharmacy refill and claims data were the most commonly used measures of adherence in research, routine practice, epidemiological and intervention studies. These methods, and their strengths and limitations have been described in this paper. *Conclusion* A multitude of indirect measures of adherence exist in the literature, however, there is no "gold" standard for measuring adherence to medications. Triangulation of methods increases the validity and reliability of the adherence data collected. To strengthen the adherence data collected and allow for comparison of data, future research and practice interventions should use an internationally accepted, operational standardized definition of medication adherence and clearly describe the medication adherence methods used.

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## Impact of findings on practice

- Currently, there is no gold standard for measuring adherence to medications. As each measure provides approximations of different aspects of medication taking, it is necessary to triangulate methods to increase the validity and reliability of data collected in both routine practice and research.
- Measures and their methods must be fully described and include internationally standardized operational definitions of medication adherence in order to facilitate comparisons between studies and settings.
- Measuring medication adherence should be an essential component of each medication review program for patients with chronic diseases.

## Introduction

Patients' sub-optimal medication taking behaviour with respect to their therapeutic regimen leads to poorer clinical outcomes and quality of life, and generates economic loss [1–3]. A recent review of approximately 80 studies showed that 16 % of patients with a new prescription did not commence their treatment [4]. Importantly, one in two patients cease treatment within the first 12 months of therapy [5]. A Cochrane review concluded that improving medication taking may have a far greater impact on clinical outcomes than advances in treatments [2]. Therefore, improving and accurately measuring medication adherence is of paramount importance for researchers and healthcare providers.

The World Health Organization (WHO) defines adherence as [6]: *"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"*. Medication adherence, which describes medication taking behaviour, is defined according to three operational, quantifiable parameters: initiation, implementation and discontinuation (which encompasses persistence) [7]. Whilst initiation and discontinuation are regarded as 'discontinuous actions', persistence and implementation are two continuous behaviours. Medication persistence is defined as *"the length of time from initiation to discontinuation of therapy measured in units of time"* [8]. Implementation compares 'two time-series in persistent patients: the prescribed medication dosing regimen and patient's medication dosing history' [7]. Adherence, which covers both medication taking regularity and continuity, can be described comprehensively only by capturing both implementation and persistence simultaneously.

Medication adherence for an individual on chronic therapy may vary with time due to a range of factors that can impact medication taking. This presents a challenge to measuring and improving medication adherence in the long term. Factors influencing medication adherence can be modelled according to five dimensions (Fig. 1) [6, 9–11].

A second challenge in measuring medication adherence lies in the assessment method. Ideally, a simple, valid and reliable method for detecting the prevalence and types of non-adherence is needed [12]. Such a method should be reproducible and specific to changes in adherence. Currently, there is no single method available with these characteristics. However, numerous methods are available to assess patient adherence each with their own specific limitations and none necessarily better than another. There is a lack of correlation and agreement between the different methods [13], and each method appears to capture different information on medication taking. Direct methods measure the ingestion of medications (e.g. pharmacological and biochemical markers) whereas indirect measures are proxy measures of medication adherence (e.g. electronic devices, self-report instruments, pill counts, pharmacy refills).

## Aim of the review

This article reviews the different methods available for measuring medication adherence in routine healthcare and research studies, with a specific focus on their strengths and weaknesses in detecting, quantifying and qualifying poor adherence.

## Method

We performed a literature review on medication adherence measures in patient populations with chronic conditions taking chronic medications. We used the following search algorithm in Medline (from May 2003 to May 2013): ((medication adherence [mesh major topic] OR patient compliance [mesh major topic]) AND medication*[title/abstract] AND (Assessment*[title/abstract] OR measure*[title/abstract])). A complementary manual search of references cited in the included studies was performed in order to identify any additional studies. We limited our initial search to reviews, meta-analyses and clinical trials. Abstracts were screened and selected if articles evaluated the validity of a method for measuring adherence and/or if they compared several measurement methods. Articles were excluded if they were not published in English, or did not assess the effectiveness of tools to measure adherence.

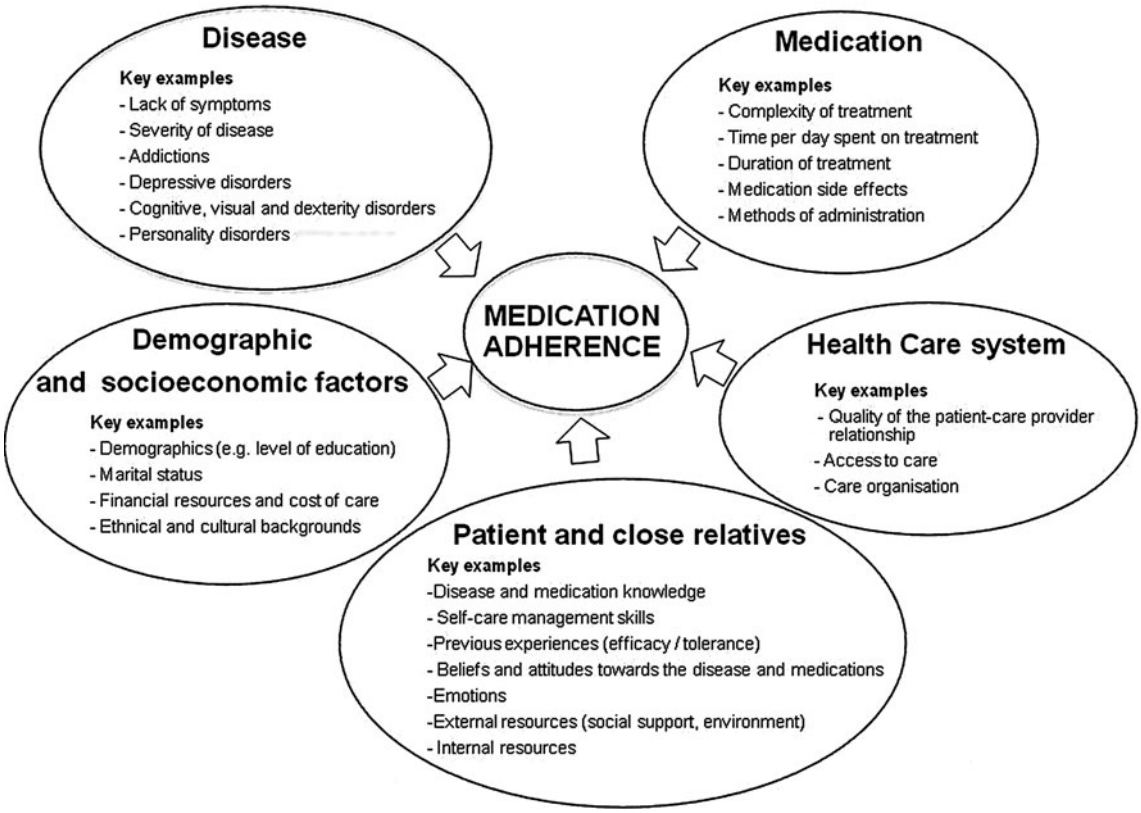


**Fig. 1** Factors influencing medication adherence in chronic patients [6, 9–11]

Of the 238 initial Medline search results, 74 papers were pre-selected from their abstract and 57 full texts were retrieved. Furthermore, 47 articles were included in this review as a result of the manual search. The retrieved full texts were classified within a table according to the measure of adherence used (see "Appendix" [1, 6, 12–113]). According to this classification, measures used were: self-report (reported in 50 publications), electronic measures (33), pharmacy refills and claims data (26) and pill counts (25). Patient self-report, electronic measures, pharmacy refill and claims data are the most commonly used measures of adherence in research, routine practice, epidemiological and intervention studies. Therefore, we focused on these methods in the review.

## Results

All available direct and indirect methods for assessing medication adherence have been described in Tables 1 [114] and 2 [13, 16, 23, 25, 41, 47, 70], respectively. Direct methods provide evidence that the patient has administered their medication. On the contrary, indirect methods are proxy methods, which do not prove administration and whose usefulness as a measure of adherence differs according to each method. Indirect methods are more numerous than direct methods and have been developed to capture the patient's behaviour as accurately as possible within their own methodological limits.

### Self-reports

Self-report measures, such as interviews, questionnaires and diaries where patients or their family members/caregivers provide information about medication taking, are currently considered as the most practical approaches to measuring adherence [1, 71, 72]. They are the most commonly used adherence measures in clinical and research settings due to their low staff and respondent burden, low cost, flexibility, relative unobtrusiveness and less time consuming to complete [26, 73, 74]. Self-report measures can gather social, situational, and behavioural data and allow exploration of beliefs which can impact adherence [30, 75]. They are able to distinguish between intentional and unintentional non-adherence [17, 76].

Whilst self-report measures are often grouped together, it is important to note that these measures vary considerably. Many have been developed for specific chronic diseases, targeting a range of patient populations, used in a variety of settings (e.g. from clinical practice to clinical trials), and differ in their format, questions and measurement scales [19, 30, 33, 38, 39, 42, 45]. This is demonstrated by Garfield who

identified 58 self-report measures, consisting of 1–21 items, using Likert or visual analogue scales [17]. Self-report measures can be used in different ways: face-to-face interview, telephone interview, self-administration and computer programmes [17, 53, 73, 74, 77]. The majority of the measures are designed for adult patients [6, 17, 76]. Only a few questionnaires explore timing variations in medication administration which is an important element to monitor in some conditions, such as organ transplantation [29]. Importantly, the targeted levels of adherence vary between 80 and 100 % [73].

**Table 1** Direct methods for assessing medication adherence

| Measure | Description | Strength | Limitations |
|---|---|---|---|
| Blood medication or metabolites monitoring | Measure of medication or metabolite level in plasma, serum or blood according to timing of blood drawn and last self-reported ingestion of medication. | Prove the ingestion of medication | Measure can be used for a limited number of medications (e.g. antiretroviral or anti-cancer medications, and those with a low therapeutic index such as digoxin and cyclosporine) |
| | | | Provide information on short-term medication adherence (dependent on medication's half-life) |
| | | | Static measure |
| | | | May be a biased measure of patient's medication taking behaviour as results refer to the days preceding blood testing |
| | | | Methods have to be standardized |
| | | | Interpretation of data depends on intra- and inter-individual medication metabolism variations |
| | | | Delay between blood testing and results. |
| | | | Costly |
| | | | Invasive |
| Urine medication or metabolites monitoring | Quantitative or qualitative determination of medication or metabolites eliminated by the kidney in a single urine sample or during a 24-h urine collection. | | Measure can be used for a limited number of medications i.e. those that are predominantly metabolized and excreted in the urine (e.g. isoniazid) |
| | | | Pharmacokinetics of the medication has to be known (i.e. absorption, excretion) |
| | | | Laborious urine collection (e.g. over a 24 h period) |
| | | | May be a biased measure of patient's medication taking behaviour as results refer to the days preceding urine collection |
| | | | Static measure |
| | | | Methods have to be standardized |
| | | | Interpretation of data depends on intra- and inter-individual medication metabolism and excretion variations |
| | | | Delay between urine collection and results. |
| | | | Costly |
| Biological markers (e.g. HbA1c*; INR**) | Biological markers determined through blood tests, which are directly affected by ingestion of medication | | Measure can be used for a limited number of medications |
| | | | Influenced by other biological parameters and patient behaviours |
| | | | Static measure |
| | | | Costly |
| | | | Invasive |
| Ingestible event marker (Proteus™) [13] | An ingestible, grain-of-sand sized microsensor fixed in each tablet, which communicates with a data recorder in the form of a skin patch, and software. It also monitors heart rate, temperature and respiration. Data can be relayed to patient's and significant other cell phones. | | Limited experience in its use |
| | | | Limited research on its use |
| | | | Ethical issues linked to the novelty of the measure and its invasiveness |
| | | | Costly |
| | | | Not specifically designed for clinical practice |

* HbA1C = Glycosylated Haemoglobin A1C

** INR = coagulation International Normalised Ratio

**Table 2** Indirect methods for assessing medication adherence

| Measure | Description | Strengths | Limitations |
|---|---|---|---|
| Self-report (e.g. self administered questionnaires, diaries, interviews), | A range of measures that determine patients' medication adherence based on self-report | As valid as pill count if completed within a defined patient-caregiver relationship<br>Easy to administer<br>Cheap<br>Possibilities of exploring different dimensions of adherence (unintentional and intentional non adherence) | Difficulties in detecting poor adherence (sensitivity) [15, 16]<br>Risk of false positive and lack of sensitivity to change due to memory recall issues (forgetfulness), and social desirability (distortion), particularly when no trust between patient and health caregiver<br>Important to validate self-report instruments<br>Medium used (e.g. paper, electronic devices, Internet) and the frequency of administration may impact data collected<br>May overestimate adherence in comparison to electronic measures, however results are moderately correlated [17, 18] |
| Electronic devices (e.g. bulky pill-bottles, blisters, inhalers) | Medication package, which is fitted with an electronic microchip that records each date and timing of the opening or activation of the device | Longitudinal measure of medication intake (date and timing of each use and non-use of the device)<br>Repeated, correlated data on medication intake over time<br>Sensitivity to change in medication taking behaviour (provides estimates of adherence close to actual behaviour)<br>Addresses particular behaviours such as the 'tooth brush effect' effect (increase in adherence immediately before and after the medical visit), and medication holidays<br>Can assess relationship with relevant clinical outcomes | Patient must consent to use the device for each single dose, or take notes of deviations (pocket doses) (if not, risk of false negatives [14])<br>Device may interfere with patient's daily life<br>Potential positive bias by reinforcing medication intake (Hawthorne effect [14]).<br>May impact patients' control of medication taking and cause anxiety; thus care should be taken in how the device is used with patients<br>Does not suit all pharmaceutical dosage forms<br>Costly |
| Pharmacy refills and prescription claims databases | Calculation of the Medication Possession Ratio (MPR) as total days' supply of medication dispensed to a patient divided by the number of days that the patient should have been taking the medication; and the proportion of days covered (PDC) calculated as the number of days on which a medication is available to the patient divided by the total number of days in the data analysis period | Used for analyzing large retrospective databases | No monitoring of medication ingestion<br>Does not reflect daily intake variation (persistence and adherence)<br>Not applicable if patients get their medication from different pharmacists or health insurers, whose databases are independent |
| Clinical outcomes | Measures of disease-specific outcomes according to good clinical practice (e.g. blood pressure, heart rate, cholesterol level, HIV viral load, cancer markers) | Adherence is a surrogate endpoint of clinical outcomes | Affected by many other factors (appropriateness of medication, biological and genetic factors, environment, patient's other behaviours, etc.)<br>Intra- and inter-variability (e.g. white coat effect when measuring blood pressure) |
| Pill count | Number of units of medication dispensed multiplied by dosage, divided by the number of tablets that should have been consumed according to dosage and number of days within analyzed period (give as a % value) | An overall or global measure of medication adherence | Static measure, which does not reflect daily variability<br>Does not prove that medication has been swallowed<br>Patients have to return pill- containers at each visit<br>Risk of 'pill dumping' before returning pill containers (risk of false positives)<br>Not accurate in detecting poor adherers [12] |
| Healthcare provider's report | Opinion of healthcare provider according to interview with the patient and interpretation of outcomes measures | Indicator but not a measure per se<br>Dependant on the quality of the relationship | Lack of reliability (like flipping a coin) and reproducibility [19]<br>Risk of false positives and negatives |
| Interviewing with significant others (e.g. family) | Qualitative, semi-structured assessment of significant others' opinion. | Indicator but not a measure per se<br>Dependant on the quality of the relationship | Not a standardized method<br>Limited reliability<br>Risks of false-positives and false-negatives |

There are several key elements that need to be considered when constructing self-report measures in order to ensure that the tools are reliable and valid. It is important that adherence tools are developed based on a theoretical framework and a qualitative exploratory phase [17], and attention is given to evaluating their psychometric properties, i.e. reliability, validity and responsiveness [78] prior to using the measures [74]. Validity can be assessed by comparing self-report against other measures of adherence such as electronic devices, pill counts and clinical markers [17]. Garber et al. [65] found that of the self-report measures, diaries and self-administered questionnaires were more likely to be concordant with other measures (such as electronic devices, pill counts/canister weight measures, plasma drug concentrations, claims data, clinical opinions) than researcher administered interviews. In 58 measures identified by Garfield et al. data about validation against other measures were presented in support of the vast majority of self-report measures (54 of the 58 measures), while the data on internal and test–retest reliability (16/58) was available for a relatively smaller number of measures and limited data were available on the acceptability of self-report measures [17].

Several studies have determined that self-report measures tend to overestimate medication adherence [12, 18, 26, 34, 47, 56, 60, 79, 80]. This could be due to two major biases. Firstly, social desirability may encourage the patient to say what they think the interviewer expects from them in line with the impression they want to create [73, 78, 80]. Secondly, memory bias or errors in self-observation can result in both over and under reporting. Patients may have difficulty remembering that they missed a dose [74]. Overall, patients who report non-adherence are likely to be telling the truth [6].

Strategies have been suggested to reduce these biases: (1) Starting the self-report measure with a statement that normalizes non-adherence by recognizing the challenges of taking regular medications [53]; (2) Carefully choosing the wording of the questions to avoid negative or positive questions which may encourage a biased response [6, 74], and avoiding ambiguous terms such as "often" or "occasionally" which can be misinterpreted [6, 74]; (3) Using data collection strategies which provide anonymity, such as on-line self-administered surveys or Computer Assisted Self-Interview [46, 74]; (4) Asking about a missed dose in the few hours or 3 days prior to data collection rather than 1 month or 1 year [78]. However two studies have suggested to using a 1 month period instead of a 3- or 7-day period [81, 82]. (5) Using diaries and self-administered questionnaires rather than interviews [65]; (6) Using a combination of adherence measures, preferably alternatives to memory recall [74] or using a complementary clinical outcome measure [62] for patients who may have impaired memory or cognitive functioning.

The advantages of self-report measures make them suitable for use in the clinical setting [1] because they allow adherence behaviour to be "qualified" by assessing the various factors that can impact patient adherence [17, 75, 76, 83] therefore helping the healthcare provider to develop a tailored medical and educational program.

## Electronic measures

Electronic measures are the only measures which allow health professionals and researchers to measure medication adherence longitudinally, in 'real time', providing a detailed dose-by-dose description for a patient. Both dimensions of adherence, implementation and persistence to treatment, can be evaluated and independently modelled over time [84]. Electronic monitoring generates data on the date and time of each opening of the bottle. Such data can be repeated and compared over time. Therefore, by using statistical analyses, such as Kaplan–Meier analysis, and mixed-effect models, persistence and implementation can be described [85]. Whilst, reducing such data to one static descriptor (e.g. percentage of days with correct dosing over the period of observation) is a commonly used and convenient way of expressing the data, this loses the dynamic information provided by electronic monitoring.

Electronic monitoring of medication adherence has allowed researchers to establish a positive association between adherence and clinical outcomes [13, 24, 86]. Dunbar-Jacob et al. [13] showed that electronic monitoring predicted clinical outcomes more accurately than self-report and pill count in lipid-lowering therapy. Electronic measures also allow changes in adherence with time to be evaluated. This provides a method for describing longitudinal behaviour and identifying trigger factors which can contribute to non-adherence.

Additionally, the data collected are also useful for the patients themselves. The data can be used to provide feedback to the patient on his/her behaviour from one visit to another [84]. By interpreting the electronic report, the patient is invited to describe what may have happened in their daily life which may have influenced medication taking. Feedback provision is a powerful method in exchanging information with the patient, understanding patients' perspectives, supporting patient adoption of a new behaviour or sustaining a behaviour change and encouraging autonomous use of medications [87]. To maximise the feedback, it is important that healthcare providers receive informed consent from the patient for their active participation, are empathic in providing feedback and educate the patient about how best to use the electronic devices and the results obtained.

It is important to reinforce the significance of collecting quality data by ensuring that there is a strong association between opening of the vial and the medication ingestion. Patients have to be informed to swallow the medication immediately after opening the vial. This emphasis can bias

the data collected, however, its influence disappears after 5–6 weeks of monitoring [16]. Moreover, it can also be argued that this acts as a transient intervention to promote adherence to medications, and its impact on clinical outcomes has to be evaluated. Whilst it is possible that patients may cheat and open the electronic device without swallowing the medication, this risk is perceived as limited, and can be minimised in clinical practice by adopting an empathic approach to patient care.

The main limitation of electronic measures is the cost of the devices, which can be balanced with the richness of data collected. The cost, however, may not make the use of the devices practical for healthcare providers in their daily practice, unless it is reimbursed by third party payers, such as health insurers or the government. Another limitation is that electronic devices do not suit every patient. Healthcare providers must confirm their user friendliness, and check that patients can accept them easily without preventing them from taking their medication. In addition to the classical bulky electronic devices (e.g. MEMS™), new devices have recently been made available. Some of them include new communication strategies through the Internet and smartphone applications [88, 89]. Some devices are easy to carry (e.g. Wisepill™ [90]), some apply to pharmaceutical forms other than tablets (e.g. SIMpill® system, MDILog™ [91], Doser® CT [91], i-Neb Nebulizer™ [92], eye-drop monitor [93]), some can monitor several medications simultaneously (e.g. Med-eMonitor® [94]), some apply directly to medication blister cards (e.g. POEMS [95], Med-ic® blister in development, from ABR Pharma, Paris, IDAS® [96], Helping Hand [97]), and some are designed for patients on polypharmacy needing extensive assistance with treatment (e.g. carousel [98]). However, continuous research and technical developments are required to transfer such devices to routine care.

### Pharmacy refills and prescription claims databases

Pharmacy refill and prescription claims data can be used to provide indirect assessments of patient adherence [99]. This data provides insight into whether patients' prescriptions have been filled and the frequency of refill [68]. By extension, the number of days that patients have been without their prescribed medications can also be determined [68]. This approach to adherence measurement is often utilized in retail pharmacy by examination of computerized patient prescription records [100], and in retrospective assessments of adherence which source prescription-related information from large pharmacy claims or insurance-based databases [58]. The time between the date that the medication was first dispensed and the projected date that the medication would run out without additional refills, is used as a proxy for adherence.

The primary outcome measure reported is the medication possession ratio (MPR) which is a standard measure of patients' possession of dispensed prescription medications over time [101]. MPR is calculated as the total days' supply of medication dispensed divided by the number of days that the patient should have been taking the medication [102]. This duration of time is defined as the number of days between a patient's first receipt of the medication and their final prescription refill during a designated period. Where the number of days' supply is equivalent to the number of days between these two time-points, the MPR will equal 1, and represent 'perfect' adherence [102]. Provided that the number of days' supply remains constant, the longer the duration of time between the first and last prescription, the lower the MPR value.

The proportion of days covered (PDC) is also another measure of adherence calculated using pharmacy refills or claims data [103]. The PDC is calculated as the number of days on which a medication is available to the patient divided by the total number of days in the data analysis period. Interestingly, MPR has been shown to overestimate adherence rates compared to PDC [103]. MPR [104] and PDC [103] values $\geq$0.8 (or 80 %) are used in most studies as the threshold value for 'adequate' adherence, thereby distinguishing those who are adherent from those who are not. This cut-off value may not necessarily be indicative of adequate clinical adherence as, depending on the medical condition and treatment in question, some or any missed doses may lead to negative health consequences [102].

In retrospective studies, persistence is assessed by determining the number of days of continuous therapy [105]. While the definition of continuous therapy differs between studies, researchers generally pre-specify a 'permissible' number of days between consecutive script refills based on the anticipated date that a patient should run out of the dispensed supply of medication [106]. A patient is considered to be persistent if refills are obtained within this pre-specified gap.

The use of pharmacy refill and claims data is advantageous as it is non-invasive [80] and can be conducted at no inconvenience to patients. The data is objective [99], readily available [68] and provides a more economical approach to estimating adherence compared to electronic measures [68]. The findings and conclusions of studies using this information are supported by strong statistical power owing to the large populations studied via these data-rich databases.

Such studies are also of great interest from an epidemiological perspective [107], as they rely on data from large populations which relate to community based samples, providing a more accurate illustration of real-world medication use as opposed to clinical trials where a controlled environment may lead to misrepresentations of adherence and persistence rates [108]. Studies have determined that adherence estimates obtained by using pharmacy refill and claims data are comparable to those

provided by electronic measures, and therefore provide a fair estimate of adherence [36].

Despite this, some argue that this approach may provide a good measure of medication possession but it does not necessarily satisfy criteria for determination of medication use [109, 110]. Furthermore, the data provide no information about the actual ingestion of a medication, daily variations in medication use or the timing of missed doses [62, 68, 72, 80, 100, 107, 109–112]; and do not provide insight into how a patients' use of medication influences clinical outcomes, due to lack of data on certain variables such as symptom severity [113]. Although in most cases the link between a patient not refilling their prescription and insufficient medication consumption can be assumed [112], there are other factors which could influence this. Patients may receive medication samples from physicians or practice pill-splitting [112], neither of which would be identified in the prescription data but could vary the frequency of refill collection.

The method is further limited by its inability to capture information about patient use of over-the-counter [68] or prescription medications from different pharmacies or health insurers whose databases are independent [62, 100]. Also, in relying on pharmacy dispensing records, the approach fails to capture any information about patients who are prescribed a medication but never get it dispensed [112]. Furthermore, as these studies rely on multiple refills of medications over time to determine adherence, it is best suited to the study of chronic treatments rather than those used for acute illnesses [68].

Overall, pharmacy refill and claims data provide only an indirect approximation of medication use and are subject to several limitations. Nevertheless, the key strength of this method is that it provides insight into medication adherence and persistence amongst large community samples, which renders it a valuable research tool, and a popular one from an epidemiological perspective. Triangulation of data with other tools can lead to more accurate estimates of treatment adherence and persistence.

## Discussion

A considerable number of publications have been devoted to the measures of medication adherence in the past 10 years. The economic and public health issues associated with medication non-adherence and the methodological complexity of the phenomenon to be assessed are probably two explanations for this finding. Indeed, we do not possess a "gold standard" for measuring adherence, hence the increasing number of assessment tools seen in the literature [12]. As it is not possible to measure actual adherence behaviour without continuous observation of patients, the majority of measures used are proxy indicators of adherence rather than absolute measures.

Amongst the methods commonly used by pharmacists and researchers to assess medication adherence, self-report, electronic measures and pharmacy refills and claims data are the ones mainly used in routine care or research studies. They are all indirect methods, with their own specific limitations but strengths which allow their continued use in research and practice. Self-reports are easy to use; electronic measures provide the most accurate measure of adherence; and pharmacy refills are the most appropriate for measuring adherence in large epidemiological studies or databases.

Each available measurement tool captures complementary information at the different stages of the medication administration process, from prescription collection to final consumption/administration. Administrative databases tell us what has been prescribed and dispensed. Electronic systems tell us longitudinally what has been removed from the packaging of the medication. Self-report measures also allow exploration of patients' beliefs, attitudes and behaviour.

In evaluating the correlation between these measures, it has been shown that there is a weak correlation between prescription refills and self-report. Others have shown that self-report measures weakly to moderately correlate with electronic measures (correlations ranged from 0.45 to 0.29) [13, 23, 25]. Garber et al. compared the self-report measures (self-administered questionnaires, diary tracking, face-to-face and telephone interviews) with measures they called "non-self-reported" (administrative claims, pill counts or canister weight, plasma drug concentrations, electronic event monitoring, or clinical opinions). Across 86 comparisons of self-report and non-self-report measures, 37 (43 %) were categorized as highly concordant. The difference in concordance by type of self-report method was significant ($p < 0.01$), diaries and self-completion questionnaires showing a higher concordance with non-self-report measures compared with interviews. On the other hand, self-report measures were less likely to be concordant with electronic measures as compared with other non-self-report measures ($p < 0.01$) [65]. Finally, it is interesting to note that the correlation between these various methods remains moderate, underlying the fact that they explore different components of medication adherence. These methods are complementary and the combination of direct and indirect methods or indirect methods together is a useful approach to increase reliability and validity of collected data. In using these methods, it is critical to acknowledge the limitations of the methods and triangulate adherence data using two or more methods.

Triangulation between complementary methods can be applied in parallel to increase accuracy of methods or sequentially for refining the screening of non-adherent patients or for further exploration of adherence related issues. For example, data collected through electronic monitoring should be reconciled with pill-counts and structured patient interviews. Pill-counts allow the healthcare provider to verify whether there is an important discrepancy with electronically measured adherence rates, while structured interviews allow the healthcare provider to explore patients' opinions on adherence before reading the results of the electronic measure with the patient. Sequential use may be useful when healthcare providers use a screening self-report measure to screen for non-adherence; non-adherent patients may then be suitable candidates for using an electronic device as an educational tool.

Finally, a dichotomous cut-off differentiating adherent from non-adherent patients has long been omnipresent alongside adherence measurements. This cut-off has been traditionally but somehow arbitrarily fixed at 80 % since Haynes studies in tuberculosis [115], and often carried through to other chronic diseases without further clinical validation. Dichotomising adherence is useful for some statistical analyses. However, it is imperative that adherence levels or thresholds are clearly defined and are appropriate for the condition and treatments under investigation. Such thresholds vary with the measure used and may not have a specific clinical meaning, especially if adherence is not correlated with clinical outcomes, quality of life, or other patient health outcomes. The strength of association between adherence and clinical outcomes is more relevant.

## Conclusion

A multitude of indirect measures of adherence exist in the literature, each with their own strengths and limitations. Triangulation of methods increases the validity and reliability of the adherence data collected.

It is important that appropriate methods are selected for the specific purposes of adherence studies or programs. Initiation of therapy is best measured when the patient returns to the health professional after the first prescription. Data on the time and frequency of visits, complemented with self-report findings, can provide information on initiation to therapy and issues surrounding medication taking. Once a patient has initiated therapy, persistence rate to treatment should be measured. Electronic monitors, self-report and pharmacy refills and prescription claims databases are the more appropriate methods for measuring persistence rates. Pharmacy refills and prescription claims databases are particularly useful in large epidemiological studies. Finally, within a persistent population, implementation can be monitored by self report or electronic monitors. The choice of the methods will also depend on the design of the study, whether it is cross-sectional or longitudinal, prospective or retrospective.

Self-report and electronic monitors can also be used as routine clinical tools: self-report for screening large samples and identifying factors that influence medication taking and identifying patients at risk of non-adherence; and electronic monitors for supporting patients with adherence issues. Identification of suboptimal adherent behaviour and its causes, are crucial for understanding the impact of non-adherence on patient clinical outcomes, as well as the economic impact to the healthcare system. An accurate measure of adherence and a thorough understanding of factors that impact a patient's medication taking assist healthcare providers in developing tailored support for individual patients to promote and optimize adherence to therapy. Adherence to chronic medications is a dynamic behaviour that can be influenced by different factors over the course of a patient's therapy. It is therefore important that researchers and health professionals continuously monitor patients' adherence.

Overall, the adherence literature is limited by the inconsistency in defining adherence and using appropriate adherence measures. In order to compare and reproduce medication adherence results, researchers and healthcare providers have to consider, firstly, using an internationally accepted operational, standardized definition of medication adherence [7]; secondly, accurately describing medication adherence methods used; and thirdly ensuring the quality, validity and reliability of the methods and data analyses employed.

**Conflicts of interest** None.

**Funding** None.

## Appendix

See Table 3.

**Table 3** Literature review on medication adherence measures in chronic diseases

| | References | Self-report | Electronic devices | Pharmacy Refill and Claims data | Specific recall* | Pill count | Blood/urine medication monitoring | Clinical outcome | Healthcare provider's report |
|---|---|---|---|---|---|---|---|---|---|
| Literature search | Vollmer et al. [14] | | | X | X | | | | |
| | Dunbar-Jacob et al. [13] | X | X | | X | X | | | |
| | McCarberg et al. [15] | X | | | | | X | | |
| | Cook et al. [16] | | X | | | | | | |
| | Garfield et al. [17] | X | | | | | | | |
| | Spoelstra et al. [18] | X | X | X | X | X | X | | X |
| | Mora et al. [19] | X | | | | | | | |
| | Vervloet et al. [20] | | X | X | X | | | | |
| | Devulapalli et al. [21] | X | | | | | | | |
| | Sajatovic et al. [22] | X | X | X | | X | X | | X |
| | Shi et al. [23] | X | X | | | | | | |
| | Nakonezny et al. [24] | X | X | | | X | | | |
| | Shi et al. [25] | X | X | | | | | | |
| | Carter et al. [26] | X | X | X | | X | | | |
| | Velligan et al. [27] | X | X | X | | X | X | | |
| | Cohen et al. [28] | X | | X | | | | | |
| | Dobbels et al. [29] | X | | | | | | | |
| | Greenlaw et al. [30] | X | X | | | | | | |
| | Muzzarelli et al. [31] | X | | | | | X | | |
| | Berk et al. [32] | X | X | | | X | X | | X |
| | Cohen et al. [33] | X | X | | | | | | |
| | Bell et al. [34] | X | X | | | | | | |
| | Velligan et al. [35] | X | X | X | | X | X | | X |
| | Hansen et al. [36] | X | X | X | | | | | |
| | Vreeman et al. [37] | X | | X | | X | X | | |
| | Zelikovsky et al. [38] | X | | | | | | | |
| | Morisky et al. [39] | X | | | | | | X | |
| Literature search | Tzeng et al. [40] | X | | | | | | | |
| | Zeller et al. [41] | X | X | | | | | | |
| | Reynolds et al. [42] | X | X | | | | | X | |
| | Gossec et al. [43] | X | X | X | | X | X | | X |
| | Cramer et al. [44] | X | X | X | | X | | X | |
| | Gehi et al. [45] | X | | | | | | X | |
| | Bender et al. [46] | X | X | | | | | | |
| | Parker et al. [47] | X | X | | | | | | X |
| | Bryson et al. [48] | | | X | | | | | |
| | Elm et al. [49] | X | | | | X | | | |
| | Wetzels et al. [50] | | X | X | | | | X | |
| | Safren et al. [51] | X | | | | | | | |
| | Escalada et al. [52] | X | X | | | X | | | X |
| | Berg et al. [53] | X | X | X | | X | X | | |
| | Hearnshaw et al. [54] | X | X | X | | X | | X | |
| | Velligan et al. [55] | X | X | X | | X | X | | X |
| | Pratt et al. [56] | X | | | | X | | X | |
| | Chia et al. [57] | X | X | X | | X | | | |

**Table 3** continued

| | References | Self-report | Electronic devices | Pharmacy Refill and Claims data | Specific recall* | Pill count | Blood/urine medication monitoring | Clinical outcome | Healthcare provider's report |
|---|---|---|---|---|---|---|---|---|---|
| | Andrade et al. [58] | | | X | | | | | |
| | Kerr et al. [59] | X | X | X | | X | | | |
| | Hess et al. [60] | X | | | | X | | | |
| | Sikka et al. [61] | | | X | | | | | |
| | Maclaughlin et al. [62] | X | | X | | X | | | |
| | Nieuwkerk et al. [63] | X | | | | | | | |
| | Dolder et al. [64] | X | | X | | | | | |
| | Garber et al. [65] | X | X | X | | X | X | | X |
| | DiMatteo [66] | X | X | X | | X | X | | X |
| | Butler et al. [67] | X | | | | | X | | X |
| | Vik et al. [68] | X | X | X | | X | X | | X |
| | Feinn et al. [69] | X | X | | | X | | | |
| Manual search (in order of appearance) | Loayza et al. [70] | X | | | | | X | | X |
| | Jay et al. [71] | | | | | X | X | | |
| | Choo et al. [72] | X | X | X | | X | | | |
| | Nunes et al. [1] | X | | | | | | | |
| | Simoni et al. [73] | X | | | | | | | |
| | Williams et al. [74] | X | X | X | | X | | | |
| | George et al. [75] | X | | | | | | | |
| | Gadkari et al. [76] | X | | | | | | | |
| | Paterson et al. [77] | X | | | | | | | |
| | World Health Organization [6] | X | X | X | | X | X | | X |
| | Kimberlin et al. [78] | X | X | X | | X | X | | |
| | Zogg et al. [79] | X | | | | | | | |
| | Horne et al. [12] | X | X | | | | | | |
| | LaFleur et al. [80] | X | X | X | | | X | X | X |
| | Lu et al. [81] | X | X | | | | | | |
| | Doro et al. [82] | X | X | | | | | | |
| | Matza et al. [83] | X | | | | | | | |
| | Krummenacher et al. [84] | | X | | | | | X | |
| | Gertsch et al. [85] | X | X | | | X | | | |
| | Burnier et al. [86] | | X | | | | | X | |
| | De Bruin et al. [87] | | X | | | | | | |
| | Dayer et al. [88] | X | X | X | X | X | X | | |
| | Broomhead et al. [89] | | X | | X | | | | |
| | Haberer et al. [90] | X | X | | | X | | X | |
| | Ingerski et al. [91] | | X | | | | | | |
| | Daniels et al. [92] | X | X | | | | | | X |
| | Hermann et al. [93] | | X | | | | | | |
| | Haberer et al. [94] | | X | | | X | | X | |
| | Arnet et al. [95] | | X | | | | | | |
| | Santschi et al. [96] | | X | | | | | | |
| | De Bleser et al. [97] | | X | | X | | | | |

**Table 3** continued

| | References | Self-report | Electronic devices | Pharmacy Refill and Claims data | Specific recall* | Pill count | Blood/urine medication monitoring | Clinical outcome | Healthcare provider's report |
|---|---|---|---|---|---|---|---|---|---|
| Manual search (in order of appearance) | Schmidt et al. [98] | X | X | X | | | | X | X |
| | Osterberg et al. [99] | X | X | X | | X | X | X | X |
| | Steiner et al. [100] | | | X | | | | | |
| | Vink et al. [101] | | | X | | | | | |
| | Watanabe et al. [102] | | | X | | | | X | |
| | McKenzie et al. [103] | | | X | | | | | |
| | Karve et al. [104] | | | X | | | | | |
| | Cramer et al. [105] | | X | X | | | | | |
| | Peterson et al. [106] | | | X | | | | | |
| | Blaschke et al. [107] | | X | | | | | | |
| | Lachaine et al. [108] | | | X | | | | | |
| | Krueger et al. [109] | X | X | X | | X | X | | |
| | Marcum et al. [110] | X | X | X | | X | | | |
| | Murray et al. [111] | X | X | X | | X | | | |
| | Jonikas et al. [112] | | | X | | | | | |
| | Palli et al. [113] | | | X | | | | X | |

* Specific recall, i.e. automated telephone reminders by short message service, smartphone medication adherence applications or acoustic reminders

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