

REVIEW

A systematic review finds inconsistency in the measures used to estimate adherence and persistence to multiple cardiometabolic medications

Sofa D. Alfian^{a,b,*}, Ivan S. Pradipta^{a,b}, Eelko Hak^a, Petra Denig^c

^aUnit Pharmacotherapy, -Epidemiology and -Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, the Netherlands

^bFaculty of Pharmacy, Department of Pharmacology and Clinical Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia

^cDepartment of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

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Abstract

Objectives: We reviewed measures used to estimate adherence and persistence to multiple cardiometabolic medications from prescription data, particularly for blood pressure-lowering, lipid-lowering, and/or glucose-lowering medication, and give guidance on which measures to choose.

Study Design and Setting: A literature search of Medline, Embase, and PsycINFO databases was conducted to identify studies assessing medication adherence and/or persistence for patients using multiple cardiometabolic medications. Two reviewers performed the study selection process independently.

Results: From the 54 studies assessing adherence, only 36 (67%) clearly described the measures used. Five measures for adherence were identified, including adherence to “all,” to “any,” to “both” medication, “average adherence,” and “highest/lowest adherence”. From the 22 studies assessing persistence, only six (27%) clearly described the measures used. Three measures for persistence were identified, including persistence with “all,” with “both,” and with “any” medication. Less than half of the studies explicitly considered medication switches when relevant.

Conclusion: From the identified measures, the “any medication” measure is most suitable for identifying patients in need of an intervention, whereas the “all medication” measure is useful for assessing the effect of interventions. More attention is needed for adequate measurement definitions when reporting on and interpreting adherence or persistence estimates to multiple medications. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Medication adherence; Persistence; Prescription data; Multiple cardiometabolic medications; Medication switch; Medication addition

1. Introduction

Adherence and persistence to preventive medication are known to be suboptimal in daily practice [1]. This is recognized as a significant public health issue because medication nonadherence leads to poor health outcomes and increased health care costs [2]. Medication adherence refers to whether patients take their medications as prescribed, whereas persistence refers to whether they continue to take the medication [3]. As patient behavior is modifiable, it is

important to assess adherence and persistence, and subsequently develop interventions to improve their medication-taking behaviors. However, most adherence measurements in intervention trials were found of low quality, which may influence the precision of adherence rates and subsequently lead to inefficient or even ineffective interventions [4].

Because of the increase rate of polypharmacy [5], it becomes very relevant to monitor adherence and persistence to multiple medications for the same indication. Adherence assessment is more complex for these patients, particularly when drugs can be switched or added over time. In addition, it is important to make a distinction between adherence and persistence. Although these are related concepts, they occur at different times of drug-taking behavior, that is, in the implementation phase or the discontinuation phase [3]. Only a patient who is still persistent (i.e., continuing

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* Corresponding author. Tel. +31 (0)50-363-7576; fax: +31 (0)50-363-2772.

E-mail address: sofa.alfian@unpad.ac.id (S.D. Alfian).

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What is new?**Key findings**

- We identified five distinct measures to estimate adherence and three distinct measures to estimate persistence in patients using multiple medications from prescription data, which can be used by future adherence researchers.
- Many studies were flawed because of inadequate description of the measures or how switching or additions were dealt with.

What this adds to what was known?

- To our knowledge, this is a first study that systematically reviews the measures used to estimate medication adherence and medication persistence to multiple medications.
- This review extends previous literature on adherence measures to multiple medications by identifying distinct measures to estimate multiple medications adherence and multiple medications persistence that may lead to different estimates.

What is the implication and what should change now?

- Researchers and practitioners need to be aware of unclear or inadequate definitions of the adherence and persistence measures when interpreting results for patients using multiple medications and targeting interventions to improve medication use.
- More attention is needed for providing adequate measurement definitions in studies reporting on adherence or persistence to multiple medications.

therapy) can be nonadherent to a medication (i.e., taking less medication) [3]. This distinction seems not always sufficiently addressed when assessing adherence to multiple medications [6,7].

The primary objective of this study is to systematically review the measures that are used to calculate adherence and persistence to multiple preventive medications from prescription data and give guidance on when and why one should choose one measure over another. We focus on cardiometabolic medication, including blood pressure-lowering, lipid-lowering, and glucose-lowering medication. The secondary objective is to assess whether studies sufficiently describe the measures used, particularly in relation to addressing issues of switching and adding medication at drug class or therapeutic level.

2. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [8] guideline to report this systematic review. This systematic review was registered in International Prospective Register of Systematic Review (PROSPERO; www.crd.york.ac.uk) with registration number CRD42017069299.

2.1. Search strategy and selection criteria

A literature search of Medline, Embase, and PsycINFO databases up to June 16, 2017 was conducted to identify studies assessing medication adherence and/or persistence to multiple cardiometabolic medications. The full search strategy using a combination of medical subject heading terms and text words can be found in the [Supplementary data](#). In short, we included experimental, cohort and case control studies among adults (age 18 years or older) that calculated medication adherence and/or persistence to multiple cardiometabolic oral medications (i.e., blood pressure-lowering, lipid-lowering, and/or glucose-lowering medication) from prescription data (i.e., prescribing, dispensing, or claims databases) and were published in English. Studies assessing adherence and/or persistence to treatment guideline or to diet, predicting adherence from model analysis, only focusing on primary nonadherence (i.e., patients not obtaining the initial prescription), assessing adherence and/or persistence from pill counts, self-report, provider or care-giver assessment, or from electronic monitoring devices were excluded. Also, studies in which the adherence and/or persistence measures were not described (i.e., measure was either not defined or only referred to another article), adherence and/or persistence measures produced non-numeric values, and case reports or abstracts from conference proceedings were excluded.

2.2. Review process

Eligibility assessment based on title and abstract was conducted independently by two reviewers (SDA, ISP). The full texts of potentially eligible articles were retrieved and reviewed in the second stage of the screening process by SDA and ISP. Disagreements between two reviewers were resolved by consensus with a third reviewer (PD). Inter-rater agreement in the title-abstract and full-text screening was calculated using percent agreement and Cohen's kappa (κ) statistic. Data from the selected articles were extracted by SDA, and any doubts from the data extraction process were resolved by consensus with ISP. We extracted the following information: country of study, study design, period of study, research question, type of data and/or database, characteristics of participants of the study (inclusion/exclusion criteria), type of medication studied, type of medication user studied (incident and/or prevalent), sample size of source population, definition of adherence and/or persistence (including the numerator and denominator, type of methods used to assess adherence

[e.g., proportion of days covered {PDC} or medication possession ratio {MPR}], any defined cutoff points and information on incorporating medication switches and/or additions at class or therapeutic level, when relevant), association of adherence or persistence measures with clinical outcomes (when presented), and funding sources.

We defined medication class level as including medication with a similar mechanism of action (e.g., sulfonylureas), whereas therapeutic level was defined as including medication with similar pharmacological effects (e.g., glucose-lowering medication). We classified the defined period for the denominator in the adherence measures as prescription-based or interval-based approach. The assessment period in a prescription-based approach is defined as the number of days between two prescriptions (variable period ending with a prescription), whereas the period in an interval-based approach is defined as the total number of days in the given

interval (fixed time interval). This distinction is relevant because the interval-based approach may lead to underestimating adherence when medication switches are not taken into account. Incident users were defined as patients who initiate medication of interest without prior use in a specified period before the measurement period, whereas prevalent users were defined as patients already taking a medication of interest before the measurement period.

2.3. Data analysis

Descriptive statistics were used to present proportions of studies with particular characteristics. We determined at study level whether measures of adherence and persistence to multiple medications were clearly defined with regard to the numerator and denominator. We also assessed whether medication switches and additions were taken into account.

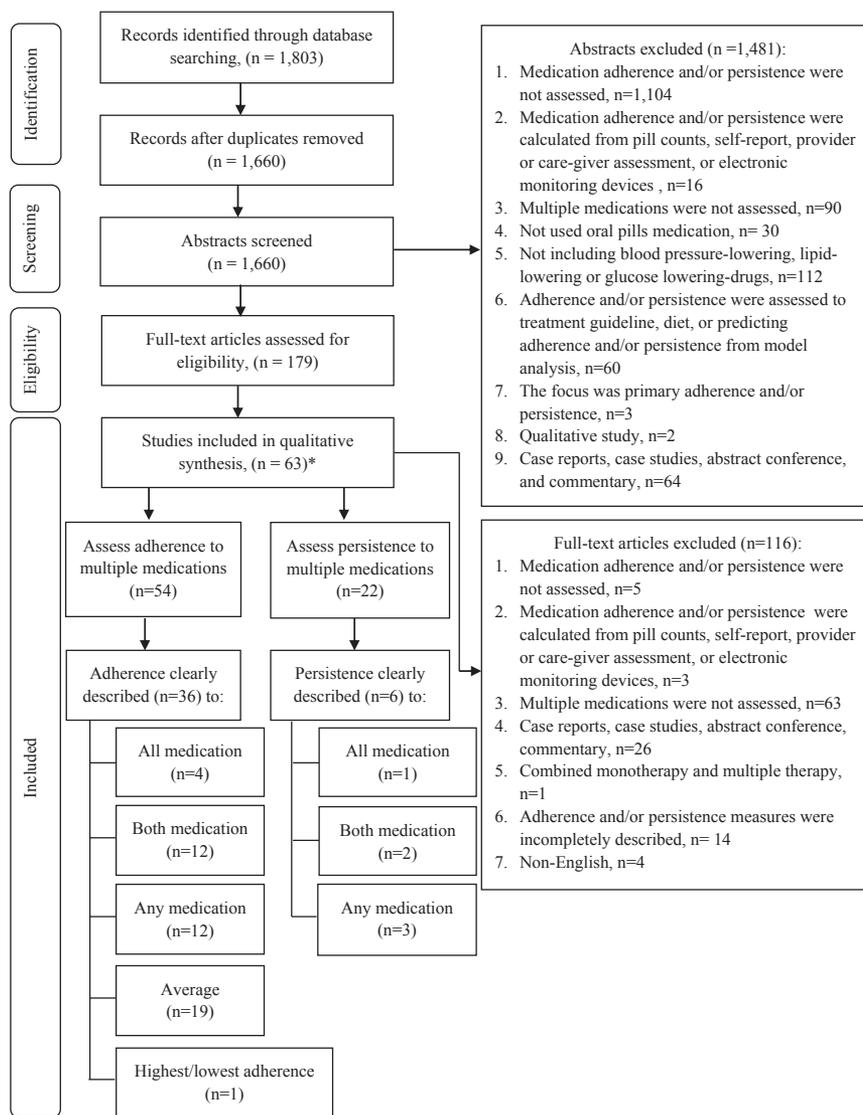


Fig. 1. Flow diagram of the systematic review process. *Several studies assessed adherence and persistence simultaneously.

Clearly defined measures were grouped to represent distinct methods of calculation.

3. Results

The literature search resulted in 1,803 records across three databases. After removing duplicates, 1,660 abstracts were screened and 179 were selected for full-text review. A total of 63 articles met the eligibility criteria (Fig. 1). The inter-rater agreement and reliability Cohen's kappa after both title-abstract and full-text screening were high (97.5% with kappa 0.88, and 98.3% with kappa 0.93, respectively). The most common medication evaluated was glucose-lowering medication ($n = 26$), followed by blood pressure-lowering medication ($n = 23$). Most of the studies were conducted using prescription data from the United States ($n = 42$). The mean sample size of source population was 68,621 participants, ranging from 568 [9] to 706,032 [10] participants. Table 1 summarizes characteristics of the studies. Study details from studies that clearly and not clearly described adherence and persistence are presented in Table S1 and S2 in Supplementary data, respectively.

3.1. Multiple medications adherence measures

Of the 54 identified studies on adherence to multiple medications, 36 studies (67%) clearly described the adherence measures with MPR or PDC as the common methods. In 31 of these 36 studies, switches or additions at class or therapeutic level were possible. Only 16 of those studies explicitly considered medication switches and/or additions [6,7,10–23]. Most of 36 studies ($n = 23$) looked at patients who initiated with one or more of the medications of interest [7,10–12,15–19,21–34]. Half of the studies ($n = 18$) used the interval-based approach [6,10,14,17–19,21,23,24,27,28,30–36], whereas 16 studies used the prescription-based approach [11–13,16,20,22,25,26,29,37–43] and two studies used both the interval- and prescription-based approach [7,15]. Of the 18 studies using the interval-based approach, only six studies took medication switching into account [6,10,14,18,33,36].

Five distinct measures to estimate multiple medication adherences were identified (Fig. 2).

First, measuring adherence to “all medications”: Four studies assessed adherence to each medication separately and defined patients as being adherent when they had collected at least 80% of each, that is, “all medications” [6,7,14,22]. All four studies assessed adherence to medication at class level, considering individual drugs within the same medication class as interchangeable, and then calculated adherence to multiple classes at therapeutic level, either for oral glucose-lowering [6,7,14] or blood pressure-lowering medication [22].

Second, measuring adherence to “both medications”: Twelve studies assessed adherence to two medications, by

Table 1. Characteristics of multiple medications adherence and/or persistence studies

Characteristics	Number of studies (%)
Country of study	
USA	42 (66.7)
Australia	2 (3.2)
Germany	3 (4.8)
Hungary	2 (3.2)
Italy	4 (6.3)
Sweden	1 (1.6)
The Netherlands	3 (4.8)
Taiwan	2 (3.2)
Hawaii	1 (1.6)
Canada	2 (3.2)
China	1 (1.6)
Sample size of source population	
500–4,999	17 (27.0)
5,000–9,999	11 (17.5)
10,000–99,999	23 (36.5)
> 100,000	12 (19.0)
Type of medication studied	
Blood pressure-lowering	23 (36.5)
Lipid-lowering	3 (4.8)
Glucose-lowering	26 (41.3)
Combination of blood pressure-, lipid-, and/or glucose-lowering medications	11 (17.5)
Type of medication users	
Incident users	32 (50.8)
Prevalent users	21 (33.3)
Incident and prevalent users	10 (15.9)

calculating the number of days when both medications were available, which was indicated by concurrent prescriptions [6,17,19,21,24,27,29–32,34,37]. Most of the studies ($n = 11$) used a value of 80% or higher to define patients as adherent, whereas one study measured adherence as a continuous variable. Eight studies assessed adherence between two drugs or two classes from the same therapeutic level (e.g., glyburide and metformin or angiotensin II receptor blockers and calcium channel blocker [CCB]) [6,21,27,29,30,32,34,37]. Four studies assessed adherence to two medications from different therapeutic levels (e.g., CCB and statin) [17,19,24,31]. To define whether drugs were considered as used concurrently, time periods need to be defined to distinguish between concurrent use and a medication switch or a medication addition. Only two studies stated this explicitly [17,21]. For example, Ferrario et al. [21], used a period of at least 60 days before discontinuation of index therapy to define a medication addition for a blood pressure-lowering medication in a class other than the index drug, whereas An and Nichol [17] defined addition as medications prescribed to treat the comorbid conditions other than the index condition during the 6-month period (index diabetes with comorbid hypertension or vice versa).

Measures	Prescription-based approach	Interval-based approach
All medications	$\frac{\text{Number of days supply of drug (class) A}}{\text{Number of days between beginning of first (a1) and end of last (a2) Rx of drug (class) A}} \geq 80\%, \text{ AND}$ $\frac{\text{Number of days supply of drug (class) B}}{\text{Number of days between beginning of first (b1) and end of last (b2) Rx of drug (class) B}} \geq 80\%, \text{ AND}$ $\frac{\text{Number of days supply of drug (class) C}}{\text{Number of days between beginning of first (c1) and end of last (c2) Rx of drug (class) C}} \geq 80\%$	$\frac{\text{Number of days' supply of drug (class) A}}{365 \text{ days}} \geq 80\%, \text{ AND}$ $\frac{\text{Number of days' supply of drug (class) B}}{365 \text{ days}} \geq 80\%, \text{ AND}$ $\frac{\text{Number of days' supply of drug (class) C}}{365 \text{ days}} \geq 80\%$
Both medications	$\frac{\text{Number of days with both drug A AND drug B available (grey blocks)}}{\text{Number of days of overlapping prescriptions (b1 to ab2)}} \geq 80\%$	$\frac{\text{Number of days with both drug A AND drug B available}}{365 \text{ days}} \geq 80\%$
Any medications	$\frac{\text{Number of days supply of drug (class) A}}{\text{Number of days between beginning of first (a1) and end of last (a2) Rx of drug (class) A}} \geq 80\%, \text{ OR}$ $\frac{\text{Number of days supply of drug (class) B}}{\text{Number of days between beginning of first (b1) and end of last (b2) Rx of drug (class) B}} \geq 80\%, \text{ OR}$ $\frac{\text{Number of days supply of drug (class) C}}{\text{Number of days between beginning of first (c1) and end of last (c2) Rx of drug (class) C}} \geq 80\%$	$\frac{\text{Number of days supply of drug (class) A}}{365 \text{ days}} \geq 80\%, \text{ OR}$ $\frac{\text{Number of days supply of drug (class) B}}{365 \text{ days}} \geq 80\%, \text{ OR}$ $\frac{\text{Number of days supply of drug (class) C}}{365 \text{ days}} \geq 80\%$
Average adherence	The average of the sum of days supply: $\frac{(\text{Number of days supply of drug (class) A} + \text{number of days supply of drug (class) B})/2}{\text{Total number of days in interval between beginning of first (a1) and end of last (a2) Rx}}$	The average of the sum of days supply: $\frac{(\text{Number of days supply of drug (class) A} + \text{number of days supply of drug (class) B})/2}{365 \text{ days}}$
	The average of adherence calculation for each medication: $\frac{\frac{\text{Number of days supply of drug (class) A}}{\text{Number of days between beginning of first (a1) and end of last (a2) Rx of drug (class) A}} + \frac{\text{Number of days supply of drug (class) B}}{\text{Number of days between beginning of first (b1) and end of last (b2) Rx of drug (class) B}}}{2}$	The average of adherence calculation for each medication: $\frac{\frac{\text{Number of days supply of drug (class) A}}{365 \text{ days}} + \frac{\text{Number of days supply of drug (class) B}}{365 \text{ days}}}{2}$
Highest or lowest adherence	$\frac{\text{Number of days supply of drug (class) A}}{\text{Number of days between beginning of first (a1) and end of last (a2) Rx of drug (class) A}} = A\%;$ $\frac{\text{Number of days supply of drug (class) B}}{\text{Number of days between beginning of first (b1) and end of last (b2) Rx of drug (class) B}} = B\%;$ $\frac{\text{Number of days supply of drug (class) C}}{\text{Number of days between beginning of first (c1) and end of last (c2) Rx of drug (class) C}} = C\%$ <p>Calculate the adherence for each medication, then taking the highest (e.g. drug class A) or the lowest (e.g. drug class B).</p>	$\frac{\text{Number of days supply of drug (class) A}}{365 \text{ days}} = A\%;$ $\frac{\text{Number of days supply of drug (class) B}}{365 \text{ days}} = B\%;$ $\frac{\text{Number of days supply of drug (class) C}}{365 \text{ days}} = C\%$ <p>Calculate the adherence for each medication, then taking the highest (e.g. drug class A) or the lowest (e.g. drug class B).</p>

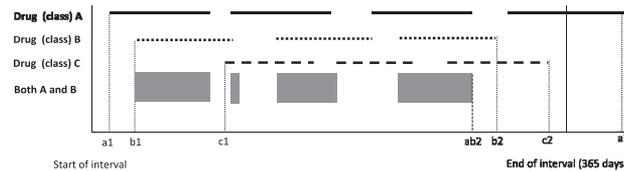


Fig. 2. Methods to estimate multiple medications adherence.

Third, measuring adherence to “any medication”: Twelve studies assessed adherence from number of days with at least one medication available and defined patients as being adherent when they had collected at least 80% of one, that is, “any medication” [6,7,14,15,18,22–24,28,33,35,38]. Also the studies using this measure first assessed adherence for medication at class level and then calculated adherence to multiple medication classes at therapeutic level for glucose-lowering [6,7,14,18,33,38], blood pressure-lowering [15,18,22–24,28,35], or lipid-lowering medication [18,28]. Two of these studies validated the proposed measure by assessing its association with clinical outcomes. The study by Tang et al. [15] showed that adherence to any blood pressure-lowering medication was inversely associated with death (OR = 0.70; 95% CI: 0.51–0.97). Fung et al. [35] showed that adherence to any blood pressure-lowering medication was associated with lower odds of having elevated systolic blood pressure (OR = 0.89; 95% CI: 0.85–0.93).

Fourth, measuring adherence by calculating the “average” adherence: 19 studies assessed adherence by first calculating adherence for the medication at individual drug level [13,20,25,26,40,42,43] or class level [6,7,10–12,14–16,35,36,39,41] and then calculate the overall average. The most common medication evaluated was glucose-lowering (n = 13), followed by blood pressure-lowering (n = 3), and lipid-lowering (n = 1) medication. Most of the studies defined adherence as an average level as 80% or more [6,7,10–16,20,25,26,35,39,43], whereas four studies reported adherence as a continuous variable [36,40–42]. Two of these studies validated the proposed measure by assessing its association with clinical outcomes. The study by Tang et al. [15] showed that the average of the class-specific adherence with an 80% cutoff level to blood pressure-lowering medication was inversely associated with death (OR = 0.71; 95% CI: 0.53–0.95). Fung et al. [35] showed that the average also with an 80% cutoff level to blood pressure-

lowering medication was associated with lower odds of having elevated systolic blood pressure (OR = 0.87; 95% CI: 0.84–0.89).

Fifth, measuring the “highest” or “lowest” adherence: One study assessed adherence to blood pressure-lowering medication by calculating adherence for each medication class, and then presented both the “highest” and the “lowest” as measure of adherence [15]. The study by Tang et al. [15], however, showed that no significant association was found between the highest or the lowest class-specific adherence and death.

3.2. Multiple medications persistence measures

Of the 22 identified studies on persistence to multiple medications, six (27%) studies clearly described the persistence measures. Only one of these studies clearly described how they dealt with medication switches [44], where switches at class or therapeutic level were possible for all studies. Three distinct measures to estimate multiple medication persistence were identified (Fig. 3).

First, measuring persistence to “all medications”: One study calculated persistence to all medications and defined patients as persistent when all medications were without a medication gap of 30 days or more [45]. Persistence was first assessed for individual drugs, and then overall persistence was defined as being persistent on all medications

from the same therapeutic level (e.g., metoprolol, hydrochlorothiazide, and amlodipine were without a medication gap) [45].

Second, measuring persistence to “both medications”: Two studies assessed persistence for two medication classes as follow: which days are covered by both classes (e.g., angiotensin II receptor blockers and CCBs) and identify whether there is a gap without coverage of both classes. Patients are considered persistent if they have no such gaps in both drug classes concurrently [30,34]. Zeng et al. [34] used a 30-day permissible gap, whereas Hsu et al. [30] used a 56-day gap to define persistence.

Third, measuring persistence to “any medication”: Two studies defined patients as being persistent when either drug class A or drug class B from the same therapeutic level were without a medication gap (e.g., ≤180 days gap) [44,46]. In other words, patients were considered nonpersistent to blood pressure-lowering medication if they were not receiving any blood pressure-lowering medication in a period of more than 180 days since the last prescription [44]. One study defined persistence to any medication by using the treatment anniversary method, that is, assessing whether or not patients are still receiving the medication in 1 year after treatment initiation. Patients were considered to be persistent if “any” (at least one) blood pressure-lowering medication was still available on the 365th day after treatment initiation [23].

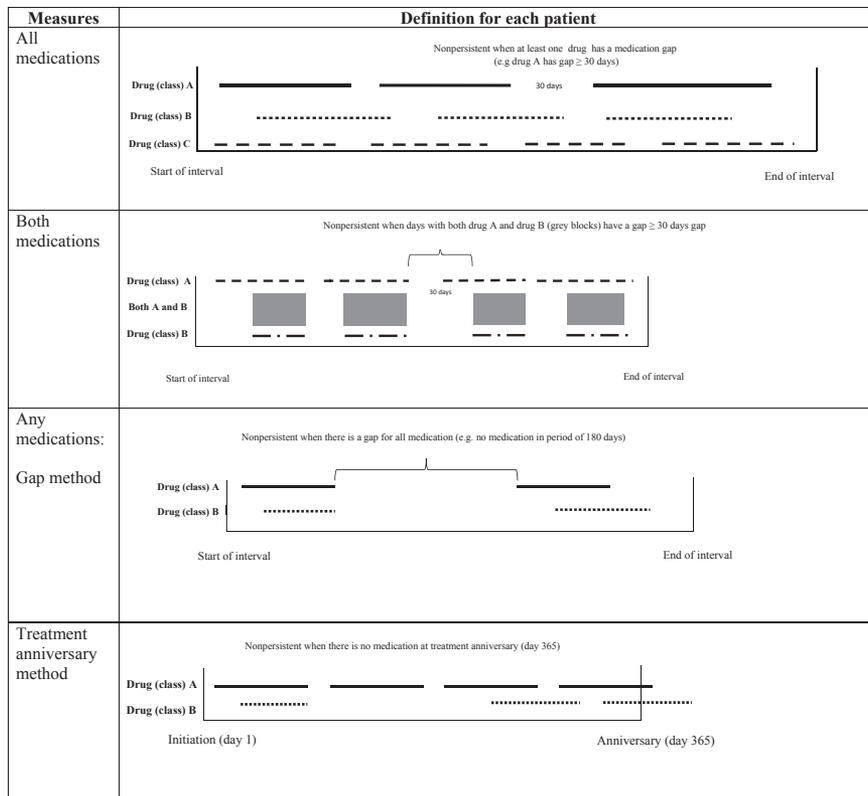


Fig. 3. Methods to estimate multiple medications persistence.

4. Discussion

We reviewed the measures that have been proposed or used to estimate medication adherence and medication persistence to multiple cardiometabolic medications. Such medication is usually intended for chronic use. From the 54 studies assessing adherence, only 36 (67%) clearly described how they calculated adherence to multiple medications. Five distinct adherence measures were identified from these studies. Of the 31 studies in which switches or additions at class or therapeutic level were possible, only 16 explicitly considered medication switches and/or additions. From the 22 studies assessing persistence, only six (27%) clearly described how they calculated persistence to multiple medications. Three distinct persistence measures were identified from these studies. Only one of the studies explicitly considered medication switches, where switches at class or therapeutic level were possible in all studies.

Most of the included studies in this review were conducted in the United States, which can in part be explained by the wide availability of longitudinal databases with prescriptions across a range of health care settings [47]. Most of studies used 80% as a cutoff point to determine adherence status, which is widely used and has shown to be a reasonable cutoff point for single drug adherence based on its ability of predicting subsequent hospitalization in diabetes, hypertension, and hyperlipidemia patients [48].

This is a first systematic literature review summarizing the measures used to calculate medication adherence and medication persistence to multiple cardiometabolic medications. This review extends previous literature on adherence measures to multiple medications [6,7], by identifying distinct measures to estimate multiple medication adherence and multiple medication persistence. Using disparate definitions, these measures will result in different estimates [6,7]. The “all medications” and “both medications” measures are very restrictive, in such a way that they will classify relatively few patients as adherent or persistent. The “all medications” measures were used in few studies, whereas the “both medications” measures were used more often, in particular to assess adherence and persistence to concurrent medication from different class or therapeutic levels. The “any medication” measure is likely to lead to relatively high adherence or persistence rates because patients are classified as adherent or persistent when they use only one of their drugs regularly. Use of the “any medication” adherence measure with an 80% cutoff level was relatively common and showed to be associated with clinical outcomes, indicating that it may be adequate for identifying clinically relevant nonadherence [15,35]. Also, the “average” adherence measure with an 80% cutoff level, which will result in intermediate scores, was common and showed to be associated with clinical outcomes [15,35]. Both the “any medication” for adherence and persistence measures and the “average” adherence

measure should only be used to medication from the same therapeutic level, assuming that these drugs are partly interchangeable regarding their therapeutic effects. The “highest” or “lowest” adherence measures showed not to be associated with clinical outcomes [15]. These measures only reflect the adherence level to one drug and do not set a benchmark by using cutoff level. As such, they seem more difficult to interpret from a clinical perspective.

Adherence to individual drug classes or adherence to any medication can be calculated with MPR or PDC for patients on multiple medications [15]. However, there is a discrepancy between MPR and PDC methods when using the “adherence to any” measure. Adding the days supply for all medications in the numerator for the MPR may lead to overestimating adherence, when a patient uses multiple medications simultaneously or switches between medications with an overlap of the new drug with the prior drug [49]. Because the PDC focusses on days with or without medication, the presence of multiple medications on the same day does not lead to such overestimations [49]. Thus, PDC is preferred for calculating adherence to multiple medications because of its lower risk of overestimation [50,51]. Alternatively, Basak et al. proposed that switches between equivalent agents should be carried forward, under the assumption that the patient was supposed to consume all medication, whereas switches between different therapeutic agents should not be carried forward, assuming that the first treatment was to be discontinued at the time of the switch [6]. We found that many studies that used the interval-based approach to calculate adherence, however, did not consider medication switches. This is a matter of concern because the interval-based approach is likely to underestimate adherence by classifying patients who switch from one drug to another during the interval as being non-adherent. This is supported by previous studies showing that the interval-based approach provides lower adherence estimates than the prescription-based approach [7,15].

This review can help researchers and practitioners in choosing the measures to estimate medication adherence and persistence to multiple medications from prescription data. To identify patients for interventions to improve their adherence, the “any medication” measure may be applied, which is more sensitive to identify nonadherence. The “average adherence” and the “highest” or “lowest” adherence measures are less suitable to identify patients for interventions. In the “average adherence” measure, the high adherence to one medication may compensate poor adherence to another medication and lead to an acceptable average for the entire regimen. This measure has shown to not only overestimate but also underestimate adherence to multiple medications [52]. The “highest” or “lowest” adherence measures only reflect the adherence level to one drug, thereby disregarding poor adherence to other drugs. On the other hand, to measure the effect of interventions to improve adherence, one may select a measure with a high specificity, such as the “all medications” measure.

Furthermore, the optimal adherence threshold may differ based on the measures used [15,48]. For single medication adherence, a threshold of 80% is commonly used. This may also be appropriate when using the “any medication” measure [15]. In contrast, when using the more stringent “all medication” or “both medications” adherence measures, a lower threshold, such as 70%, might be preferred, assuming that this is sufficient to achieve the desired clinical effect. In addition, the association of adherence level with clinical outcomes may also differ based on the dose and type of medication used [53]. Higher adherence threshold for low-dose medications might be preferred than for high-dose medications to obtain a similar clinical effect. In persistence studies, the focus can be either on persistence of the initial medication/medication class or on any medication to treat a condition. To monitor whether patients are still being treated for their condition, the “any medication” and “treatment anniversary” measures may suffice because they are not restricted to a particular medication. The “treatment anniversary” measure, however, is not sensitive to early discontinuation followed by a restart before the treatment anniversary. To measure the effect of interventions on persistence, one may select the more specific “all medication” measure.

Furthermore, we found that a substantial number of studies were flawed because of inadequate description of the methods or how switching or additions were dealt with. More than 10 years ago, a checklist was developed for medication adherence and persistence studies using retrospective databases, recommending the researchers to provide a rationale and/or a formula for studies using multiple medications and explain how the analysis handled patients who switched to another medication [54]. Our study illustrates that the implementation of those recommendations is still insufficient. Therefore, both authors and reviewers of articles on adherence or persistence should pay more attention that adequate measurement definitions are provided. In addition, researchers and practitioners need to be aware of these shortcomings when interpreting results for patients using multiple medications. Both the quality of the studies and the quality of the reporting will determine whether appropriate interpretations can be made and relevant interventions can be developed.

Some strengths and limitations of our review should be mentioned. We conducted a systematic search using three databases but only considered articles published in English and studies using prescription data from prescribing, dispensing, or claim databases (health insurance). We did not include studies using electronic devices. The use of multiple electronic devices is impractical for patients using multiple medications. Therefore, it is usually decided to monitor just one medication with electronic devices in interventional studies, and hence there are too few studies using such data for multiple drug use. Two reviewers assessed the study eligibility and the inter-rater agreement for this was high. We found only two studies that analyzed the

association of adherence or persistence measures with clinical outcomes. Therefore, future studies are needed to validate the various multiple medications adherence and persistence measures with clinical outcomes. In addition, more studies are needed comparing these prescription-based measures with other methods to get better insight into potential underestimations of adherence and persistence. For example, linking prescription data with medical records could reduce some of the risk of overestimating nonpersistence when medication is stopped by the prescriber, and reasons for stopping are documented.

5. Conclusion

A variety of measures has been proposed or used to estimate adherence and persistence to multiple medications. The “any medication” measure is helpful to monitor adherence and persistence and to identify patients in need of an intervention. The “all medication” measure is more useful for assessing the effect of interventions. Many studies were flawed because of inadequate description of methods or how switching or additions were dealt with. Researchers and practitioners need to be aware of these shortcomings when interpreting results for patients using multiple medications. More attention is needed for providing adequate measurement definitions in reporting on adherence or persistence to multiple medications.

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Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jclinepi.2018.12.003>.

References

- [1] Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract* 2008;62:76–87.
- [2] Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int* 2015;2015:1–12.
- [3] Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppert T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* 2012;73:691–705.
- [4] Jeffery RA, Navarro T, Wilczynski NL, Iserman EC, Keepanasseril A, Sivaramalingam B, et al. Adherence measurement

- and patient recruitment methods are poor in intervention trials to improve patient adherence. *J Clin Epidemiol* 2014;67:1076–82.
- [5] Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. *BMC Med* 2015;13:74.
 - [6] Basak R, McCaffrey DJ, Bentley JP, Przybyla SM, West-Strum D, Banahan BF. Adherence to multiple medications prescribed for a chronic disease: a methodological investigation. *J Manag Care Pharm* 2014;20:815–23.
 - [7] Choudhry NK, Shrank WH, Levin RL, Lee JL, Jan SA, Brookhart MA, et al. Measuring concurrent adherence to multiple related medications. *Am J Manag Care* 2009;15:457–64.
 - [8] Moher D, Liberati A, Tetzlaff J, Altman DG, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Plos Med* 2009;6:e1000097.
 - [9] Shaya FT, Du D, Gbarayor CM, Frech-Tamas F, Lau H, Weir MR. Predictors of compliance with antihypertensive therapy in a high-risk medicaid population. *J Natl Med Assoc* 2009;101:34–9.
 - [10] Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy* 2008;28:437–43.
 - [11] Lo-Cigamic W-H, Donohue JM, Thorpe JM, Perera S, Thorpe CT, Marcum ZA, et al. Using machine learning to examine medication adherence thresholds and risk of hospitalization. *Med Care* 2015;53:720–8.
 - [12] Lokhandwala T, Smith N, Sternhufvud C, Sorstadius E, Lee WC, Mukherjee J. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs loose-dose combination of oral anti-diabetes drugs. *J Med Econ* 2015;19:203–12.
 - [13] Piette JD, Heisler M, Ganoczy D, McCarthy JF, Valenstein M. Differential medication adherence among patients with schizophrenia and comorbid diabetes and hypertension. *Psychiatr Serv* 2007;58:207–12.
 - [14] Sacks NC, Burgess JF, Cabral HJ, McDonnell ME, Pizer SD. The effects of cost sharing on adherence to medications prescribed for concurrent use: do definitions matter? *J Manag Care Spec Pharm* 2015;21:678–87.
 - [15] Tang KL, Quan H, Rabi DM. Measuring medication adherence in patients with incident hypertension: a retrospective cohort study. *BMC Health Serv Res* 2017;17:1–17.
 - [16] Gaddi A, Benedetto D, Capello F, Di Pietro C, Cinconze E, Rossi E, et al. Oral antidiabetic therapy in a large Italian sample: drug supply and compliance for different therapeutic regimens. *Public Health* 2014;128:70–6.
 - [17] An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. *Med Care* 2013;51:879–87.
 - [18] Beadles CA, Farley JF, Ellis AR, Lichstein JC, Morrissey JP, DuBard CA, et al. Do medical homes increase medication adherence for persons with multiple chronic conditions? *Med Care* 2015;53:168–76.
 - [19] Chapman RH, Yeaw J, Roberts CS. Association between adherence to calcium-channel blocker and statin medications and likelihood of cardiovascular events among US managed care enrollees. *BMC Cardiovasc Disord* 2010;10:29.
 - [20] Cheong C, Barner JC, Lawson KA, Johnsrud MT. Patient adherence and reimbursement amount for antidiabetic fixed-dose combination products compared with dual therapy among Texas medicaid recipients. *Clin Ther* 2008;30:1893–907.
 - [21] Ferrario CM, Panjabi S, Buzinec P, Swindle JP. Clinical and economic outcomes associated with amlodipine/renin–angiotensin system blocker combinations. *Ther Adv Cardiovasc Dis* 2013;7:27–39.
 - [22] Hedna K, Hakkarainen KM, Gyllenstein H, Jönsson AK, Sundell KA, Petzold M, et al. Adherence to antihypertensive therapy and elevated blood pressure: should we consider the use of multiple medications? *PLoS One* 2015;10:1–14.
 - [23] Lauffenburger JC, Landon JE, Fischer MA. Effect of combination therapy on adherence among US patients initiating therapy for hypertension: a cohort study. *J Gen Intern Med* 2017;32:619–25.
 - [24] Agarwal S, Tang SSK, Rosenberg N, Pettitt D, McLaughlin T, Joyce A, et al. Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? *Am J Ther* 2009;16:119–26.
 - [25] Barner JC. Adherence to oral antidiabetic agents with pioglitazone and metformin: comparison of fixed-dose combination therapy with monotherapy and loose-dose combination therapy. *Clin Ther* 2011;33:1281–8.
 - [26] Bartlett LE, Pratt N, Roughead EE. Does tablet formulation alone improve adherence and persistence: a comparison of ezetimibe fixed dose combination versus ezetimibe separate pill combination? *Br J Clin Pharmacol* 2017;83:202–10.
 - [27] Baser O, Andrews LM, Wang L, Xie L. Comparison of real-world adherence, healthcare resource utilization and costs for newly initiated valsartan/amlodipine single-pill combination versus angiotensin receptor blocker/calcium channel blocker free-combination therapy. *J Med Econ* 2011;14:576–83.
 - [28] Benner JS, Chapman RH, Petrilla AA, Tang SSK, Rosenberg N, Schwartz JS. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. *Am J Heal Pharm* 2009;66:1471–7.
 - [29] Blonde L, Wogen J, Kreilick C, Seymour AA. Greater reductions in A1C in type 2 diabetic patients new to therapy with glyburide/metformin tablets as compared to glyburide co-administered with metformin. *Diabetes Obes Metab* 2003;5:424–31.
 - [30] Hsu CI, Hsiao FY, Wu FLL, Shen LJ. Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: a population-based cohort study. *Int J Clin Pract* 2015;69:729–37.
 - [31] Hussein MA, Chapman RH, Benner JS, Tang SSK, Solomon HA, Joyce A, et al. Does a single-pill antihypertensive/lipid-lowering regimen improve adherence in US managed care enrollees? *Am J Cardiovasc Drugs* 2010;10:193–202.
 - [32] Kamat SA, Bullano MF, Chang CL, Gandhi SK, Cziraky MJ. Adherence to single-pill combination versus multiple-pill combination lipid-modifying therapy among patients with mixed dyslipidemia in a managed care population. *Curr Med Res Opin* 2011;27:961–8.
 - [33] Kirkman MS, Rowan-Martin MT, Levin R, Fonseca VA, Schmittdiel JA, Herman WH, et al. Determinants of adherence to diabetes medications: findings from a large pharmacy claims database. *Diabetes Care* 2015;38:604–9.
 - [34] Zeng F, Patel BV, Andrews L, Frech-Tamas F, Rudolph A. Adherence and persistence of single-pill ARB/CCB combination therapy compared to multiple-pill ARB/CCB regimens. *Curr Med Res Opin* 2010;26:2877–87.
 - [35] Fung V, Huang J, Brand R, Newhouse JP, Hsu J. Hypertension treatment in a Medicare population: adherence and systolic blood pressure control. *Clin Ther* 2007;29:972–84.
 - [36] Yoon J, Ettner SL. Cost-sharing and adherence to antihypertensives for low and high adherers. *Am J Manag Care* 2009;15:833–40.
 - [37] Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. *Am J Heal Pharm* 2007;64:1279–83.
 - [38] Juarez DT, Ma C, Kumasaka A, Shimada R, Davis J. Failure to reach target glycated a1c levels among patients with diabetes who are adherent to their antidiabetic medication. *Popul Heal Manag* 2014;17:218–23.
 - [39] Lau DT, Nau DP. Nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Int Classif* 2004;27:2149–53.

- [40] Nau DP, Chao J, Aikens JE. The relationship of guideline-concordant depression treatment and patient adherence to oral diabetes medications. *Res Soc Adm Pharm* 2005;1:378–88.
- [41] Thayer S, Arondekar B, Harley C, Darkow TE. Adherence to a fixed-dose combination of rosiglitazone/glimepiride in subjects switching from monotherapy or dual therapy with a thiazolidinedione and/or a sulfonylurea. *Ann Pharmacother* 2010;44:791–9.
- [42] Vanderpoel DR, Hussein MA, Watson-Heidari T, Perry A, Hons M. Adherence to a fixed-dose combination of rosiglitazone/plaate/pletformin hydrochloride in subjects with type 2 diabetes plellitus: a retrospective database analysis. *Clin Ther* 2004;26:2066–75.
- [43] Doró P, Benko R, Kosik E, Matuz M, Tóth K, Soós G. Utilization of oral antihyperglycemic drugs over a 7-year period (1998-2004) in a Hungarian population and adherence to drug therapy. *Eur J Clin Pharmacol* 2005;61:893–7.
- [44] Tu K, Campbell NRC, Duong-Hua M, McAlister FA. Hypertension management in the elderly has improved: Ontario prescribing trends, 1994 to 2002. *Hypertension* 2005;45:1113–8.
- [45] Hromadkova L, Heerdink ER, Philbert D, Bouvy ML. Association between concomitant psychiatric drug use, and patients' beliefs about and persistence with chronic cardiovascular medication. *Int J Clin Pract* 2015;69:328–35.
- [46] Wong MCS, Kong APS, So WY, Tse SLA, Wang HHX, Jiang JY, et al. Pharmacoepidemiological profiles of oral hypoglycemic agents among 28,773 Chinese patients with diabetes. *Diabetes Res Clin Pract* 2012;96:319–25.
- [47] Crystal S, Akincigil A, Bilder S, Walkup JT. Studying prescription drug use and outcomes with medicaid claims data: strengths, limitations, and strategies. *Med Care* 2007;45:S58–65.
- [48] Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Curr Med Res Opin* 2009;25:2303–10.
- [49] Raebel MA, Schmittiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. *Med Care* 2013;51:S11–21.
- [50] Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *Ann Pharmacother* 2009;43:36–44.
- [51] Malo S, Aguilar-Palacio I, Feja C, Lallana MJ, Rabanaque MJ, Armesto J, et al. Different approaches to the assessment of adherence and persistence with cardiovascular-disease preventive medications. *Curr Med Res Opin* 2017;33:1329–36.
- [52] Arnet I, Abraham I, Messerli M, Hersberger KE. A method for calculating adherence to polypharmacy from dispensing data records. *Int J Clin Pharm* 2014;36:192–201.
- [53] de Vries FM, Voorham J, Hak E, Denig P. Prescribing patterns, adherence and LDL-cholesterol response of type 2 diabetes patients initiating statin on low-dose versus standard-dose treatment: a descriptive study. *Int J Clin Pract* 2016;70:482–92.
- [54] Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Heal* 2007;10:3–12.