VALUE IN HEALTH 22 (2019) 139–156

Available online at www.sciencedirect.com

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ISPOR Report

Methods for Measuring Multiple Medication Adherence: A Systematic Review—Report of the ISPOR Medication Adherence and Persistence Special Interest Group

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ABSTRACT

Background: A broad literature base exists for measuring medication adherence to monotherapeutic regimens, but publications are less extensive for measuring adherence to multiple medications. **Objectives:** To identify and characterize the multiple medication adherence (MMA) methods used in the literature. **Methods:** A literature search was conducted using PubMed, PsycINFO, the International Pharmaceutical Abstracts, the Cumulative Index to Nursing and Allied Health Literature and the Cochrane Library databases on methods used to measure MMA published between January 1973 and May 2015. A two-step screening process was used; all abstracts were screened by pairs of researchers independently, followed by a full-text review identifying the method for calculating MMA. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed to conduct this systematic review. For studies that met the eligibility criteria, general study and adherence-specific characteristics and the number and type of MMA measurement methods were summarized. **Results:** The 147 studies that were included originated from 32 countries, in 13 disease states. Of these studies, 26 used proportion of days covered, 23 used medication possession ratio, and 72 used self-reported questionnaires (e.g., the Morisky Scale) to assess MMA. About 50% of the studies included more than one method for measuring MMA, and different variations of medication possession ratio and proportion of days covered were used for measuring MMA. **Conclusions:** There appears to be no standardized method to measure MMA. With an increasing prevalence of polypharmacy, more efforts should be directed toward constructing robust measures suitable to evaluate adherence to complex regimens. Future research to understand the validity and reliability of MMA measures and their effects on objective clinical outcomes is also needed.

Keywords: measurement method, medication adherence, medication possession ratio, persistence, polypharmacy, proportion of days covered, self-reported measures

Introduction

Medication nonadherence affects the health of individuals and influences the function of health care systems.[1] It has been shown to increase the risk of hospitalization, number of emergency department visits, and rate of mortality,[2] some of which may have been delayed, reduced, or avoided had patients remained adherent. On a global level, poor adherence also causes a financial

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1098-3015/$36.00 - see front matter

https://doi.org/10.1016/j.jval.2018.08.006

burden on already scarce resources of health care systems. In the United States alone, the total cost associated with medication nonadherence has been estimated to be between $100 and $300 billion a year.[3]

Accurately measuring medication adherence remains a clinical and research challenge. The proliferation of methods in recent years underlines the importance of measuring medication adherence not only for identifying barriers to medication-taking but also for developing interventions to address these barriers. Ensuring accurate measurement of medication adherence can help improve patients' health outcomes and reduce health care spending.

Most publications for measuring medication adherence and associating adherence with positive outcomes have focused on the use of a single medication or monotherapeutic regimen.[4–6] Some methods include directly observing patients consuming medications, pill counting, monitoring through electronic pill dispensers, and measuring adherence through outcomes such as serum drug concentration levels. Other medication adherence measurement methods pertain to clinical and administrative claims data, registries, patient and provider surveys, self-report questionnaires and scales, patient diaries, electronic and paper medical records, charts, and pharmacy records.[7,8] These methods include several measures such as medication possession ratio (MPR), proportion of days covered (PDC), time to discontinuation, persistence rate, medication gaps, composite adherence score, and the Morisky Medication Adherence Scale (MMAS).[8,9]

When patients' medication regimens involve multiple medications (polypharmacy) prescribed for the same or multiple conditions, the challenge of accurately measuring medication adherence is compounded by the complexity that arises from intermixing the dosing and timing schedules of each drug as their combined effects manifest into a single treatment regimen. The prevalence of polypharmacy is becoming increasingly common as more medications are developed to manage diseases, particularly chronic conditions. More than 30% of the global population has more than five acute or chronic conditions requiring multiple medications[10]; as for the United States, approximately 50% of the adults have one or more chronic condition, whereas one in four has two or more chronic conditions.[11] This percentage is expected to increase as life expectancy increases. Therefore, it is crucial to understand how the methods of measuring medication adherence in monotherapy would translate into polypharmacy. Moreover, as the proportion of people with multiple medical conditions increases, treatment regimens are likely to become more complex with a greater variety of therapeutic and pharmacologic options available. Thus, multiple medication adherence (MMA) methods need to account for such complexity in regimens involved in polypharmacy.

To date, a systematic review of the literature that describes how MMA has been measured has not been performed. Therefore, there is a need to review and describe methods used to examine MMA. This systematic review aimed to identify and compare the measures used for MMA found in the literature. In addition, this review will explore the extent of use of MMA measures in various disease conditions.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines to conduct and report this systematic review.[12]

Study Selection Criteria

We selected studies that included participants who used two or more concurrent medications for any acute or chronic medical condition(s). No limitations were applied to the selection of studies based on any specific intervention, control treatment, study type, or the characteristics of the study population. Only studies reporting any measure assessing MMA for a medical condition were included. Studies were excluded if they did not assess MMA. Hence, studies that were limited to measuring adherence to a single medication including fixed-dose combination medications were not included. If studies did not mention the evaluation method for medication adherence, they were considered ineligible. Studies evaluating adherence to guidelines or adherence to nonpharmacological treatment (e.g., diet and exercise) were excluded. Randomized controlled trials, observational studies (including retrospective, prospective, and cross-sectional studies), and other experimental studies examining and reporting MMA were included. Studies that reported an algorithm for testing or validating MMA measures were also considered. Conference proceedings, reviews, dissertations, book chapters, case studies, editorials, and letters were excluded because they were not considered as original research. In addition, studies were selected only if they were initially identified from a database search or a subsequent manual review of citations in selected articles. The criteria were applied throughout the selection process, including the initial selection, which consisted of a broad automated literature search of selected information about published articles and a manual review of their references, a manual selection process that included an initial review of the abstracts, and a final review of the full text.

Literature Search

Initial selection of the studies began with a literature search using PubMed, PsycINFO, the International Pharmaceutical Abstracts (IPA), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library databases on studies published between January 1, 1973, and May 13, 2015. The search was limited to only those studies that involved humans and were reported in English. While undertaking this systematic review, we did not distinguish between medication adherence and persistence, although the two terms have been used for two slightly different aspects of medication-taking behavior. Medication adherence or compliance typically refers to "the extent to which the patient acts in accordance with the prescribed interval and dose of a dosing interval," whereas medication persistence is defined as "the duration of time from medication initiation to discontinuation".[13] Although authors of the studies included in our systematic review may not have distinguished between adherence and persistence, the exact formula used to measure them was recorded whenever available. The search strategy used both Medical Subject Headings terms and text words to create search strings for adherence, polypharmacy, measurement methods, and multiple disease conditions. Some of the search terms included "adherence," "compliance," "persistence," "polypharmacy," "multiple therapies," "overlapping prescriptions," "Morisky Scale," "proportion of days covered," "medication possession ratio," "comorbidity," and "multicomorbidity." The exact search strategy used for each database is given in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.08.006. Additional relevant studies were obtained by manual searches of the reference lists of initially selected studies. Because this initial selection searched multiple electronic databases, this step ended with the consolidation of citations from all sources into a unique listing.

Selection of Studies

The citations were investigated during the initial selection process, which included an automated literature search and a manual search. The consolidated listing was divided evenly among seven pairs of reviewers to complete the manual screening

process. During the initial review, each reviewer independently assessed the content from titles and abstracts of assigned articles against the common eligibility and predefined selection criteria to decide whether there was enough information to warrant a request for the full text of an article for final review. During the final review, each reviewer again independently evaluated the full text of assigned articles against the inclusion criteria, extracting predetermined data elements in the standardized template. For both the initial and final reviews, the pairs shared their independently gathered data and resolved any disagreements by consensus, with additional consultations with a study lead if necessary. The selection process was documented with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

Data Extraction

Data extraction was done by seven pairs of reviewers, with each reviewer independently extracting data elements into the standardized template developed by the research team. The data elements in the standardized template included general study and adherence-specific characteristics. The general characteristics included type of study design; region where the study was conducted; sample size; publication year; participant's age, sex, and ethnicity; study period; diseases investigated; and types and names of medications included in the study. The adherence-specific characteristics included the terms used for medication adherence, the data sources, the nature (e.g., clinical or nonclinical in nature) of the metric, the number of measurement methods, and description of the method of measurement of adherence. To simplify reporting of data collection method and measurement methods, we used the term "administrative data" to cover similar terms when some others may have used them to refer to the same collection method. It is the term we used to cover administrative claims, pharmacy claims data, prescription refill records, administrative pharmacy records, medical claims, and electronic medical records. The term "self-report" was used when a citation may have specifically stated a measurement method as questionnaire, survey, collaterally reported (e.g., nurse/physician/caregiver), or having used an instrument.

Data Analysis

Descriptive statistics on study designs, sample size, disease conditions, specific adherence formulas, and other characteristics were reported. In addition, the number and percentage of studies using unique MMA measurements were summarized. The authors recognize the importance of including robust high-quality articles in this systematic literature review. Nevertheless, because the purpose was to identify specific methods used to measure MMA, assessment of methodological quality or risk of bias was outside the scope of this review and therefore was not reported.

Results

Literature Search

The literature search resulted in 1706 records across the five databases with an additional 8 being identified through the manual search of the reference lists of the initially selected articles and a discussion among reviewers at each step of the review (Fig. 1). After removing duplicates, we screened titles and abstracts of 1382 records, resulting in 301 potentially eligible articles for full-text review. After reviewing relevant full texts, 154 articles were excluded, mainly because either the evaluation method of medication adherence was not described (n = 53) or the study did not assess MMA (n = 84). Data were extracted from the remaining 147 studies for this analysis, the first of which was published in 1990 and almost 58% being published in 2010 or later. In the three decades since the first publication, 4 were published in the 1990s, 57 in the 2000s, and 85 between 2010 and 2015. No articles were published between 1970 and 1989.

Study Characteristics

The general characteristics of included articles are presented in Table 1. Of the included articles (n = 147), 127 were observational studies (57 retrospective cohort, 45 prospective cohort, and 25 cross-sectional), 19 randomized controlled trials, and 1 validation study. The articles originated from 32 countries that were grouped geographically into seven regions, with most of the studies being conducted in the United States (n = 85). The mean sample size was 10,284 participants, ranging from 3[14] to 597,190[15], with a mean age varying between 15[16] and 87 years[17] and an overall mean age of 54.56 years. Articles encompassed 13 different medical conditions, with the most frequent diseases being HIV/AIDS (n = 45) and cardiovascular diseases (n = 43).

Study-specific details from the full-text review are presented in Table 2. The details include study design, sample size, country, diseases studied, methods used to collect data to measure adherence, and methods of calculating adherence for multiple medications.

MMA Measures

All included studies investigated medication adherence to more than one medication (Table 1); nevertheless, in 57.8% of the studies (n = 85), the exact number of evaluated medications was not reported. In almost half the articles (n = 70, 47.6%), only the number of medication classes was available instead of the number and names of actual medications prescribed. Out of 147 qualifying articles, 74 (50%) studies used more than one method to measure MMA. The most common measures for evaluating MMA were self-reported multi- or single-item questionnaires (n = 72 [49.0%]), PDC (n = 26 [18.0%]), and MPR (n = 23 [15.6%]) (Table 3).

Utilization-Based MMA Measures

In studies that used electronic data records, several different measures were applied for calculating adherence, including variations of MPR, PDC, and missing days or doses calculations (Table 4). Formulas for derivation of MPR and PDC varied between studies; 9 different versions were used for MPR and 10 were used for PDC (Table 4).

Self-Reported MMA Measures

More than half the studies (n = 78, 53.1%) used a self-report method for measuring MMA (Table 3). The most commonly applied self-reported measure was the MMAS (4-/8-/9-item version), which was applied in 21 studies (14.3%) (Table 4).

MMA Measures and Disease Conditions

Application of adherence measures varied across disorders. For cardiovascular disorders, PDC was the most commonly used adherence measure; nevertheless, for sexually transmitted disorders (e.g., HIV/AIDS), self-reported methods were preferred (Fig. 2).

Discussion

This systematic literature review summarizes the MMA measures used in articles published from January 1, 1973, to May 13, 2015. We found that the first article on MMA was published in 1990 and

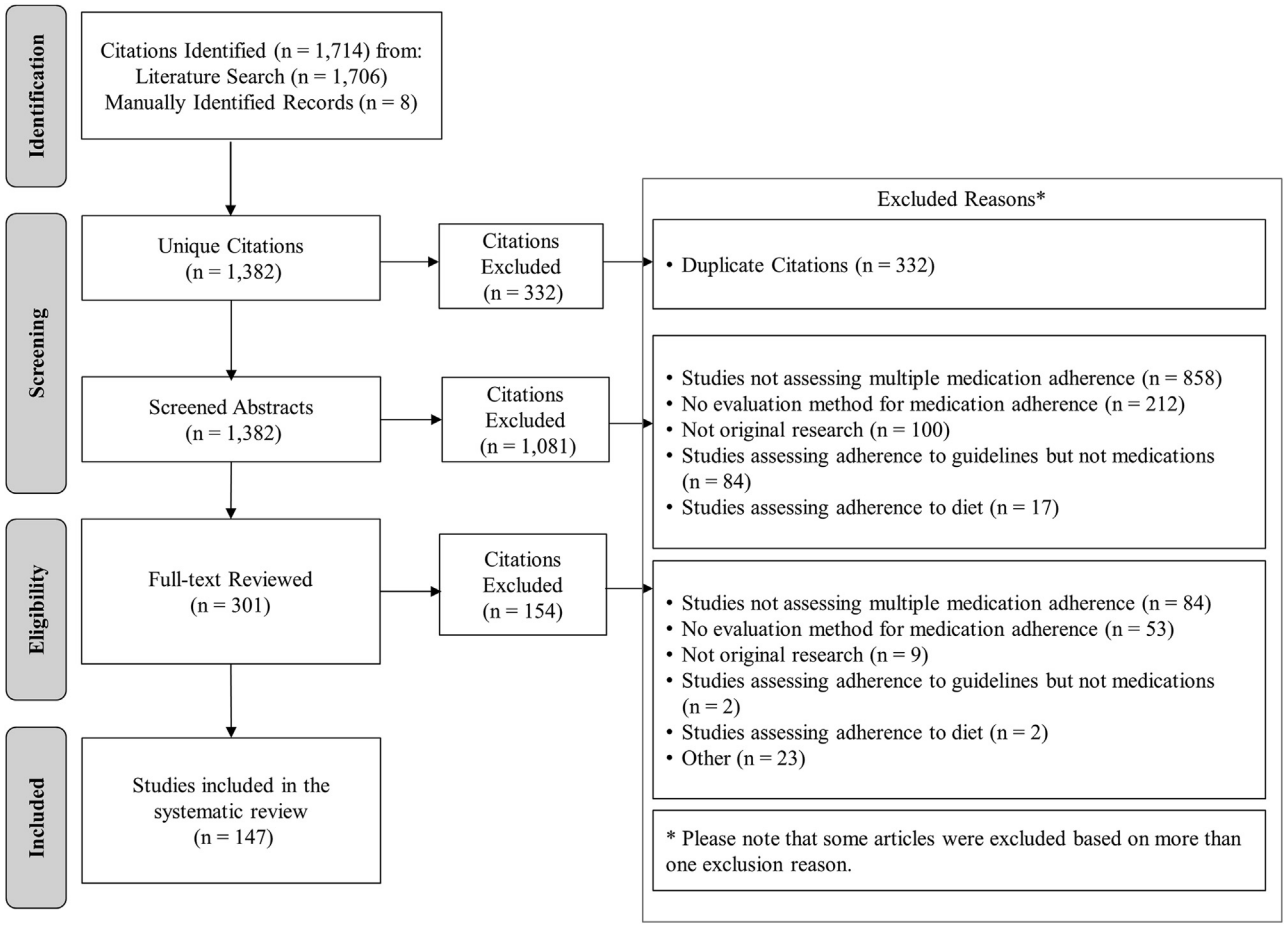

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

as per our knowledge, there is no systematic review that exclusively assesses MMA measures used in the literature. Previous systematic reviews reported MMA measures in the context of adherence-improving interventions, but none addressed measurement of MMA as their primary focus.[18–21]

Measures based on patient self-report could be simple, inexpensive, and straightforward and therefore can be conveniently administered in research and clinical practice settings. This view potentially explains why more than 50% of the studies included MMA measures based on self-report. Within the self-reported measures, there were 32 different MMA measures, with MMAS being used in the largest number of studies (21 studies, or 14.3%). The dominance of MMAS as an MMA measure is perhaps not surprising given that the MMAS is a well-established measure and because its concurrent and predictive validities have been well documented.[9,22] It is also important to note that some self-reported measures are designed for specific diseases. For example, we found multiple HIV/AIDS-specific MMA measures including the Adult AIDS Clinical Trial Group Adherence to Combination Therapy Guide, Community Programs for Clinical Research on AIDS Adherence Form, and Swedish HIV Cohort Study—Adherence Questionnaire. As found by Nguyen et al.,[23] the underlying motivations behind the use of different self-reported measures are whether the goal of the study is to shed light on medication-taking behavior, to understand barriers to medication adherence, and to elicit patients' beliefs about medicine. Nevertheless, medication adherence methods based on self-report are not without criticism. Many authors have identified that self-reported methods have the potential of over-reporting adherence or failing to disclose nonadherence due to recall bias, missing data, social desirability concerns, and faults in self-observation.[24–26] Another criticism identified in our literature review is the large volume of self-reported measures used, which leads to difficulties in making comparisons between studies. Indeed, research has shown poor agreement between self-reported measures of adherence.[27–30] Only a few studies combined self-reported measures with database measures such as MPR and PDC. In addition, there was a difference in verbiage used to solicit self-reported adherence. Medication adherence is a complex behavior involving initiation of therapy, implementing a dosing regimen and persisting with treatment.[31] These separate facets of adherence behavior are not currently captured in self-reported measures. It is also often not clear what aspect of adherence behavior is captured in self-reported measures.

Like self-reported measures, MPR- and PDC-based MMA measures also had multiple variants. For example, there were 9 MPR-based submeasures and 10 PDC-based submeasures. There is a subtle distinction between operationalizing PDC and MPR, where the PDC numerator is the sum of covered days and the numerator for MPR is the sum of days supplied. In addition, 24 (16.3%) studies calculated some disparate MMA measures. The wide variation in MPR- and PDC-based MMA measures could potentially be attributed to study design (e.g., retrospective vs. prospective study), data availability, potential subjectivity in opting for one specific method versus others, clinical judgment, or the complexity of the underlying treatment patterns such as titration, augmentation,

Table 1 – General characteristics of MMA studies included in the systematic review (N = 147).

Characteristic	No. of studies, n (%)
Types of studies	
Observational studies	127 (86.4)
Cross-sectional	25 (17.0)
Prospective cohort	45 (31.0)
Retrospective cohort	57 (38.8)
Randomized controlled trial	19 (12.9)
Validation study	1 (0.7)
Geography	
North America	87 (59.2)
Europe	38 (25.8)
Asia	10 (6.8)
Africa	3 (2.0)
Oceania (Australia and New Zealand)	3 (2.0)
Middle East	3 (2.0)
Latin America	1 (0.7)
Not reported	2 (1.4)
Sample size	
<100	20 (13.6)
100–999	61 (41.5)
1000–4999	30 (20.4)
>5000	36 (24.5)
Age groups	
Mean age <65 y	89 (60.5)
Mean age ≥65 y	33 (22.4)
Not reported	25 (17.0)
Disease areas/disorders*	
HIV/AIDS	45 (30.6)
Cardiovascular	43 (29.2)
Metabolic	20 (13.6)
Mental	14 (9.5)
Musculoskeletal	8 (5.4)
Cancer	5 (3.4)
Neurological	5 (3.4)
Respiratory	4 (2.7)
Infection (not HIV)	3 (2.0)
Transplant	3 (2.0)
Dermatological	2 (1.4)
Gastrointestinal	2 (1.4)
Urological	2 (1.4)
Not reported	7 (4.8)
Number of medications patients received	
>1–5 medications	43 (29.3)
>5–10 medications	13 (8.8)
>10 medications	6 (4.1)
Not reported if a patient received >1 medication	85 (57.8)
Adherence data collection methods†	
Self-report method	78 (53.1)
Administrative claims	58 (39.5)
Clinical measures	16 (10.9)
Electronic medication monitoring	9 (6.1)
Pill count	7 (4.8)
Electronic medical records	5 (3.4)
Patient's appointment records	3 (2.0)
Other methods	2 (1.4)
Pharmacy claims	1 (0.7)
Prescription refill records	1 (0.7)
Not reported	1 (0.7)

MMA, multiple medication adherence.
* Some studies included patients with multiple disease conditions.
† Some studies included more than one adherence data collection method.

and switching. Different adherence definitions have been shown to lead to qualitatively different conclusions. As mentioned by Choudhry et al.,[32] the choice of a specific MMA measure might hinge on why adherence is being evaluated. The lack of standardization in MMA measures found in the literature often prevents conducting meta-analyses in which multiple studies can be pooled to assess the effect of interventions for medication adherence.[33] Future research is needed to assess the appropriateness of the derivations of measurements outlined in the previous sections because this was outside the scope of the present review and therefore not evaluated.

The existence of heterogeneous MMA measures renders comparison of studies a challenge, suggesting that simulation or other follow-up studies need to be conducted to assess the existing measures in terms of their ability to measure true MMA. Quantifying the effect each measure has on true MMA may enable us to factor in the underestimation or overestimation of bias each method has on MMA measurement. The importance of such standardized MMA measures will increase in coming years because approximately one in every four persons in the United States has more than two chronic conditions.[11] In addition, single conditions are also commonly being treated with multiple medications. It has been shown that medication adherence not only improves clinical outcomes but also leads to decrease in avoidable adverse events and health care utilization, resulting in lower costs.[34–37] In addition, having the ability to estimate such standardized MMA measures would help identify at-risk patient populations in real time, which in turn can help deploy adherence-improving interventions by health systems including health insurance or prescription drug plans.[38,39]

Our review also underscores the need for the pharmacoeconomics and outcomes research community to develop a checklist or guidelines with regard to the minimum reporting criteria involving MMA studies similar to Peterson et al.,[40] who focused primarily on adherence to monotherapy. For example, a substantial number of studies (87, or 57.6%) did not report the number of medications upon which the reported MMA measure was based. Such studies then become very difficult to replicate using the same or other data, thereby making them redundant for any policymaking guidelines. A checklist would ensure that a certain minimum quality is met and maintained across all future studies of MMA.

We also found that the prevalence of MMA measures was higher in some specific disease groups. For example, 43 (29.2%) studies pertained to cardiovascular disease area, whereas 45 (30.6%), 20 (13.6%), and 14 (9.5%) studies were in the areas of HIV/AIDS, metabolic diseases, and mental health conditions, respectively. It can be speculated that this pattern could potentially be an artefact of how these or related diseases manifest in patients often requiring combination therapy, which is why the prevalence of MMA measures in these disease areas seems to be higher than in others.[41] In terms of specific MMA methods used, MPR, PDC, and patient-reported outcome questionnaires were used somewhat in equal numbers in cardiovascular diseases, whereas patient-reported outcome and other self-reported MMA measures dominated mental health conditions potentially because of convenience of administering measures based on self-report to patients with mental health issues.

This study has several limitations. First, this systematic review considered only articles published in English. Second, the systematic review profiled the MMA measures used for more than four decades; nevertheless, the study was not designed to find out the best MMA measures, and therefore cannot recommend one measure over another. Limitations exist with each of the measures of medication adherence, and some are well known. For instance, MPR as commonly calculated has been reported to overestimate adherence by considering overlapping days of

Table 2 – MMA-specific characteristics of the studies included in the review.

Study	Study design	Sample size	Country	Diseases investigated	Data collection methods	Measurement methods
Amruth et al.[43]	Retrospective cohort	240	India	Epilepsy	Self-report	Questionnaire
Arnet et al.[14]	Algorithm validation study	3	Switzerland	Not reported	Administrative data	1 MPR 2 Daily polypharmacy possession ratio
Arnsten et al.[44]	Prospective cohort	67	United States	HIV/AIDS	1 Self-report 2 Electronically monitored	1 Questionnaire 2 MEMS
Belderok et al.[45]	Prospective cohort	945	The Netherlands	Malaria	Self-report	Daily diary entries
Billimek et al.[46]	Retrospective cohort	1,369	United States	Diabetes	Self-report	Questionnaire
Bobes et al.[47]	Prospective cohort	895	Spain	Schizophrenia	Self-report	Missed doses
Bramlage et al.[48]	Prospective cohort	14,526	European: Austria, Belgium, Germany, The Netherlands, and Switzerland	Hypertension	1 and 2 Self-report 3 Clinical measures	1 MMAS-8 2 Questionnaire 3 Blood pressure
Chan et al.[49]	Prospective cohort	361	Singapore	Cancer	Self-report	Daily diary entries
Chapman et al.[50]	Retrospective cohort	4,052	United States	Dyslipidemia and hypertension	Administrative data	1 PDC 2 PDC threshold
Choudhry et al.[51]	Retrospective cohort	33,646	United States	First MI episode	Administrative data	PDC
Choudhry et al.[32]	Retrospective cohort	7,567	United States	Diabetes	Administrative data	1 Average PDC 2 Proportion of days with ≥1 drug available 3 Proportion of patients with PDC ≥80% for all drugs
Choudhry et al.[52]	Randomized controlled trial	5,855	United States	Acute MI	Administrative data	1 MPR MPR threshold
Choudhry et al.[53]	Randomized controlled trial	4,117	United States	Acute MI	Administrative data	1 PDC 2 PDC threshold
Cocohoba et al.[54]	Retrospective cohort	15,933	United States	HIV/AIDS	Administrative data	1 MPR 2 MPR threshold
Cohen and Gongvatana[55]	Randomized controlled trial	526	United States	Diabetes	1 Administrative data 2 and 3 Self-report	1 MPR 2 Summary of Diabetes Self-Care Activities scale including one medication item 3 MMAS-4
Dale et al.[56]	Prospective cohort	138	United States	HIV/AIDS	Self-report	Questionnaire
Dezii[57]	Retrospective cohort	3,942	United States	Hypertension	Administrative data	Persistence
Doró et al.[58]	Retrospective cohort	38,855	Hungary	Type 2 diabetes mellitus	Administrative data	1 MPR 2 MPR threshold 3 Refill frequency
Duong et al.[59]	Retrospective cohort	149	France	HIV/AIDS	1 Self-report 2 and 3 Clinical measures	1 PMAQ 2 Protease inhibitor levels 3 HIV viral load
Esposti et al.[60]	Retrospective cohort	19,124	Italy	Hypertension	Administrative data	Persistence
Fabunmi et al.[61]	Retrospective cohort	6,300	United States	Diabetes	Administrative data	1 MPR 2 Persistence
Farley[62]	Retrospective cohort	27,888	United States	Schizophrenia	Administrative data	PDC
Ferrario et al.[63]	Retrospective cohort	24,663	United States	Hypertension	Administrative data	1 PDC 2 PDC threshold 3 Persistence
Fincke et al.[64]	Prospective cohort	1,256	United States	Not reported	Self-report	Custom method
Flynn et al.[65]	Retrospective cohort	1,407	United Kingdom	Ischemic stroke	Administrative data	1 Persistence 2 PDC
Fung et al.[66]	Retrospective cohort	84,929	United States	Hypertension	1 and 2 Administrative data 3 Clinical measures	1 PDC • ≥1 hypertension medication • Full hypertension regimen 2 PDC threshold 3 Blood pressure
Gallagher et al.[67]	Prospective cohort	118	Australia	Heart failure and COPD	Self-report	Pill count
Gandhi et al.[68]	Prospective cohort	424	United States	HIV/AIDS	Self-report	Custom method
Gao et al.[69]	Randomized controlled trial	403	United States	Rapid-cycling bipolar disorder	Patient's appointment records	Missed appointments
Garden et al.[70]	Randomized controlled trial	231	United States	Cancer	1 Administrative data 2 Clinical measures 3 Patient's appointment records	Custom method
Gardner et al.[71]	Randomized controlled trial	1,397	United States	HIV/AIDS	Self-report	The 7-d CPCRA Adherence Self-Report Form
George et al.[72]	Cross-sectional	91	Tanzania	HIV/AIDS	1 Self-report 2 Clinical measures	1 MMAS-4 2 Saliva concentrations of nevirapine
Gianotti et al.[73]	Cross-sectional	2,114	Italy	HIV/AIDS	Self-report	Questionnaire
Giordano et al.[74]	Retrospective cohort	1,357	United States	HIV/AIDS	Self-report	CPCRA Antiretroviral Medication Self-Report instrument

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Table 2 – *continued*

Study	Study design	Sample size	Country	Diseases investigated	Data collection methods	Measurement methods
Glass et al.[75]	Retrospective cohort	7,466	Switzerland	HIV/AIDS	Self-report	The Swiss HIV Cohort Study adherence questionnaire
Grant et al.[76]	Cross-sectional	128	United States	Diabetes	Self-report	Telephone-based interviews
Guerin et al.[77]	Prospective cohort	10,570	United States	Acute coronary syndrome	Administrative data	1 Persistence rate 2 Time to discontinuation
Hansen et al.[78]	Retrospective cohort	100,556	Denmark	Osteoporosis	Administrative data	1 MPR 2 MPR threshold 3 Persistence
Hardy et al.[79]	Randomized controlled trial	19	United States	HIV/AIDS	1 Self-report 2 Pill count 3 Electronically monitored 4 Self-report, pill count, and MEMS	1 Question 2 Counting the pills remaining in the bottles 3 MEMS; cumulatively at 3 and 6 wk 4 Composite adherence score
Harzke et al.[80]	Cross-sectional	137	United States	HIV/AIDS	Self-report	Custom method
Hasford et al.[81]	Prospective cohort	13,763	Germany	Hypertension	Administrative data	1 Persistence 2 Persistence rate
Ho et al.[82]	Retrospective cohort	3,998	United States	Ischemic heart disease and diabetes	Administrative data	1 Average PDC 2 PDC threshold
Ho et al.[83]	Retrospective cohort	10,447	United States	Coronary disease	Administrative data	1 Average PDC 2 PDC threshold
Hommel et al.[84]	Randomized controlled trial	40	United States	Inflammatory bowel disease	1 Pill count 2 Self-report 3 Administrative data	1 Pill count 2 Treatment Regimen Adherence Questionnaire 3 MEMS
Ingersoll and Heckman[85]	Cross-sectional	120	United States	HIV/AIDS	1 Not reported clearly 2 Self-report 3 Electronic medical record 4 Data on proportion of medications taken, self-report, and electronic medical record	1 Percentage of medications taken out of the prescribed number 2 Medication Adherence Form 3 Collateral report of adherence 4 Summary measure of adherence
Jokisalo et al.[86]	Cross-sectional	1,561	Finland	Hypertension	Self-report	Questionnaire
Jones-Caballero et al.[87]	Prospective cohort	1,628	Spain	Acne	Self-report	Questionnaire
Jordan et al.[88]	Prospective cohort	100	Vietnam	HIV/AIDS	1 and 2 Self-report 3 and 4 Clinical measures	1 Questionnaire 2 VAS response threshold 3 $CD4^+$ cell count 4 HIV viral load
Jorgensen et al.[89]	Retrospective cohort	961	Denmark	Ovarian or peritoneal cancer	Administrative data	Custom method
Juday et al.[90]	Retrospective cohort	2,460	United States	HIV/AIDS	Administrative data	Persistence
Juday et al.[91]	Cross-sectional	461	United States	HIV/AIDS	Self-report	Questionnaire
Kalyango et al.[92]	Prospective cohort	1,256	Uganda	Malaria	Self-report Pill count	1 Caregiver's reports 2 Pill count 3 Caregiver's reports and pill count in the medicine packet
Kamat et al.[93]	Retrospective cohort	38,847	United States	Cardiovascular diseases	Administrative data	1 PDC 2 PDC threshold
Karadag et al.[94]	Prospective cohort	193	Turkey	Schizophrenia, delusional disorder, and psychotic disorder	Administrative data	Custom method
Kim et al.[95]	Retrospective cohort	380	United States	Not clearly defined (long-term users of anti-inflammatory, immunosuppressant, cancer, and multiple sclerosis medications)	Administrative data	1 PDC 2 Time to discontinuation 3 Persistence rate
Kleeberger et al.[96]	Cross-sectional	539	United States	HIV/AIDS	Self-report	Adult AIDS Clinical Trial Group adherence instrument
Kong et al.[97]	Retrospective cohort	7,034	United States	HIV/AIDS	Administrative claims	1 PDC 2 PDC threshold
Kreitchmann et al.[98]	Prospective cohort	393	Latin America	HIV/AIDS	Patient's appointment records	Gaps
Krousel-Wood et al.[17]	Cross-sectional	87	United States	Hypertension	1 Self-report 2 and 3 Administrative data	1 MMAS-8 2 MPR 3 Gaps
Lambers et al.[99]	Prospective cohort	102	The Netherlands	HIV/AIDS	1 Self-report 2 Electronic medical records	1 Missed doses 2 Viral load

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Table 2 – *continued*

Study	Study design	Sample size	Country	Diseases investigated	Data collection methods	Measurement methods
Latry et al.[100]	Retrospective cohort	594	France	Coronary artery disease	Administrative data	1 Continuous multiple-interval measures of medication availability or CMA 2 Persistence
Lau et al.[101]	Cross-sectional	301	China	Hypertension, diabetes, heart disease, hyperlipidemia, arthritis, osteoporosis, and cataract	Self-report	MMAS-4
Le Moing et al.[102]	Prospective cohort	1,203	France	HIV/AIDS	1 Self-report questionnaire 2 Clinical measures 3 Electronic medical records	1 Adult AIDS Clinical Trial Group Adherence to Combination Therapy Guide 2 Viral load
Lee et al.[103]	Retrospective cohort	86	China	Hypertension, cardiac problems, diabetes, hyperlipidemia, arthritis, and other chronic disorders	Self-report	MMAS-8, Chinese version
Letourneau et al.[16]	Randomized controlled trial	34	United States	HIV/AIDS	1 and 2 Self-report 3 Clinical measures	1 Questionnaire 2 Response threshold 3 HIV viral load
Li et al.[104]	Cross-sectional	144	United States	Hypertension	1 Self-report 2 Clinical measures	1 MMAS-4 2 Blood pressure
Li et al.[105]	Cross-sectional	202	China	HIV/AIDS	Self-report	CPCRA
Liu et al.[106]	Prospective cohort	108	United States	HIV/AIDS	1 Self-report 2 Clinical measures 3 MEMS	Custom method
Liu et al.[107]	Prospective cohort	128	United States	HIV/AIDS	1 Self-report 2 Electronically monitored, pill count, Self-report 3 and 4 Clinical measures	1 Questionnaire 2 Composite adherence score 3 $CD4^+$ count nadir 4 Peak viral load, HIV RNA, log 10
Llabre et al.[108]	Prospective cohort	323	United States	HIV/AIDS	1 and 2 Self-report 3 Electronically monitored	1 Adult AIDS Clinical Trial Group Adherence to Combination Therapy Guide 2 Medication Adherence Training Instrument 3 MEMS
Mannheimer et al.[109]	Prospective cohort	515	United States	HIV/AIDS	Self-report	Case adherence index
Mansur et al.[110]	Prospective cohort	212	Israel	Not clearly defined (elderly)	Self-report	Interview
Markotic et al.[111]	Cross-sectional	100	Bosnia and Herzegovina	Chronic nonmalignant pain	Self-report	MMAS-4
Marti et al.[112]	Prospective cohort	308	United States	Not reported	Self-report	Medical Outcomes Study Specific Adherence Scale
Mateo et al.[113]	Prospective cohort	82	Spain	Diabetes	1 Self-report 2 Pill count	1 MMAS-4 2 Pill count
Mazzaglia et al.[114]	Retrospective cohort	18,806	Italy	Hypertension	Administrative data	1 PDC 2 PDC categories 3 Cardiovascular risk, comorbidity
McLaughlin et al.[115]	Retrospective cohort	2,714	United States	Erectile dysfunction	Administrative data	MPR
Molloy et al.[116]	Retrospective cohort	165	United Kingdom	Coronary artery disease	Self-report	MARS
Monane et al.[117]	Retrospective cohort	8,643	United States	Hypertension	Administrative data	1 PDC 2 PDC threshold
Morris et al.[118]	Randomized controlled trial	492	United States	Hypertension	1 Administrative data 2 Self-report	1 MPR 2 Interview
Mosca et al.[119]	Prospective cohort	54	Portugal	Not clearly defined (elderly)	Self-report	MMAS-4
Muntner et al.[120]	Retrospective cohort	2,695	United States	Coronary artery disease	Administrative data	1 PDC 2 PDC threshold
Nekhlyudov et al.[121]	Retrospective cohort	9,818	United States	Cancer	Self-report	Custom method
Nurutdinova et al.[122]	Retrospective cohort	9,003	United States	HIV/AIDS	Administrative data	PDC
O'Carroll et al.[123]	Prospective cohort	62	United Kingdom	Stroke	1 Self-report 2 Electronically monitored	1 MARS 2 MEMS
O'Connor et al.[124]	Prospective cohort	5,295	Not recorded	HIV/AIDS	Self-report	CPCRA Medication Adherence Self-Report Form (Form 065)
Oh et al.[125]	Prospective cohort	1,102	United States	HIV/AIDS	Self-report	Dichotomized adherence
Ohl et al.[126]	Retrospective cohort	20,301	United States	HIV/AIDS	Administrative data	1 PDC 2 Gaps
Parada et al.[127]	Cross-sectional	302	United States	Diabetes	Self-report	MMAS-4
Patel et al.[128]	Retrospective cohort	4,703	United States	Hypertension and hyperlipidemia	Administrative data	1 PDC 2 PDC threshold 3 Time to discontinuation 4 Persistence rate 5 MPR

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Table 2 – *continued*

Study	Study design	Sample size	Country	Diseases investigated	Data collection methods	Measurement methods
Patel et al.[129]	Prospective cohort	50	United States	Hypertension	1 Self-report 2 Administrative data	1 MMAS-4 2 PDC
Perera et al.[130]	Randomized controlled trial	28	New Zealand	HIV/AIDS	1 Self-report 2 Administrative data 3 Clinical measures	1 MARS 2 Custom method 3 HIV viral load
Petrakis et al.[131]	Randomized controlled trial	254	United States	Alcohol dependence	Electronically monitored	MEMS
Phatak and Thomas[132]	Cross-sectional	250	United States	Not clearly defined (chronic conditions)	Self-report	MMAS-9
Pratt et al.[29]	Cross-sectional	260	United Kingdom	HIV/AIDS	Self-report	1 MMAS-4 2 RAMS 3 PAM
Pratt et al.[133]	Randomized controlled trial	72	United States	Schizophrenia and other serious mental illnesses	1–3 Self-report 4 Pill count	1 MARS 2 VAS 3 Multnomah Community Ability Scale 4 Pill count
Rintamaki et al.[134]	Cross-sectional	204	United States	HIV/AIDS	Self-report	PMAQ Revised
Ritter and Alexander[135]	Retrospective cohort	28	United States	Parkinson disease	Chart review	Refill count
Rodis and Kibbe[136]	Prospective cohort	17	United States	HCV infection	Self-report	1 MMAS-4 2 BMQ 3 Telephone interviews
Rolnick et al.[137]	Retrospective cohort	31,636	United States	Asthma, COPD, cancer, depression, diabetes, hypercholesterolemia, hypertension, multiple sclerosis, and osteoporosis	Administrative data	MPR MPR threshold
Sajatovic et al.[138]	Retrospective cohort	32,993	United States	Bipolar disorder	Administrative data	MPR
Sanfelix-Gimeno et al.[139]	Retrospective cohort	7,462	Spain	Coronary artery disease	Administrative data	1 PDC 2 PDC threshold
Sanglier et al.[140]	Retrospective cohort	4,552	United States	Depression	Administrative data	1 MPR 2 MPR categories
Sankaranarayanan et al.[141]	Cross-sectional	556	United States	Solid organ transplant	Self-report	Patient self-reported Immunosuppressant Therapy Adherence Scale
Schmid-Mohler et al.[142]	Cross-sectional	114	Switzerland	Immunosuppressive medication in renal transplant	Self-report	1 Basel Assessment of Adherence Scale for Immunosuppressives 2 Questionnaire
Schuz et al.[143]	Prospective cohort	309	Germany	Geriatrics	Self-report	RAMS
Schuz et al.[144]	Prospective cohort	215	Germany	Geriatrics	Self-report	RAMS
Scott and Pope[145]	Prospective cohort	98	Not recorded	Mood disorder	Self-report	Tablet Routines Questionnaire
Sension et al.[146]	Randomized controlled trial	81	United States	HIV/AIDS	Self-report	PMAQ-7, version 1.1
Shaya et al.[147]	Prospective cohort	568	United States	Hypertension	Administrative data	1 MPR 2 MPR threshold
Sicras-Mainar et al.[148]	Prospective cohort	2,067	Spain	Diabetes mellitus	1 and 2 Prescription refill records 3 Clinical measures	1 Compliance 2 Persistence 3 Hb A_{1c} monitoring
Sicras-Mainar et al.[149]	Prospective cohort	5,630	Spain	MDD	Administrative data	Persistence
Smith et al.[150]	Randomized controlled trial	1,857	United States	HIV/AIDS	1 Self-report 2 Clinical measures	1 Single self-report item 2 HIV viral load
Sorensen et al.[151]	Cross-sectional	204	Australia	Multiple medical conditions	1 Self-report 2 Clinical measures	1 Questionnaire: could be the Duke Severity of Illness Checklist
Spoelstra et al.[152]	Retrospective cohort	822	The Netherlands	Type 2 diabetes	Administrative data	1 Medication Intervals 2 Medication Totals 3 Medication Out 4 Compliance categories 5 Compliance dichotomy
Staehelin et al.[153]	Prospective cohort	4,654	Switzerland	HIV/AIDS	Self-report	Swiss HIV Cohort Study Adherence Questionnaire
Sung et al.[154]	Retrospective cohort	772	United States	Hyperlipidemia	1 Self-report 2 Administrative data	1 MMAS-4 2 Compliance 3 Compliance dichotomy
Tan et al.[155]	Retrospective cohort	24,438	United States	Acne vulgaris	Administrative data	1 MPR 2 MPR threshold

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Table 2 – *continued*

Study	Study design	Sample size	Country	Diseases investigated	Data collection methods	Measurement methods
Tan et al.[156]	Retrospective cohort	3,905	United States	Anxiety, depression, bipolar disorder, schizophrenic disorders, other nonorganic psychoses, adjustment disorders, and personality disorders	Administrative data	PDC
Taniguchi et al.[157]	Cross-sectional	624	United States	HIV/AIDS and MDD	Self-report	1 VAS 2 VAS categorized
Tantikosoom et al.[158]	Cross-sectional	160	Thailand	Cardiovascular disease	Self-report	MMAS-8, Thai version
Tennant et al.[159]	Retrospective cohort	389	United States	HIV/AIDS	1 Administrative data 2 Self-report	1 Adherence 2 Adherence threshold 3 Self-report adherence 4 Self-report adherence threshold
The RISC Group[160]	Randomized controlled trial	796	Sweden	Coronary artery disease	Clinical measures	Measurement of platelet aggregation
Tsai et al.[161]	Retrospective cohort	193	Taiwan	Geriatric	Electronic medical records	Unspecified
van Boekel et al.[162]	Prospective cohort	75	The Netherlands	Renal transplant	Self-report	Questionnaire
van Bruggen et al.[163]	Randomized controlled trial	1,283	The Netherlands	Type 2 diabetes mellitus	Administrative data	MPR
van der Linden et al.[15]	Retrospective cohort	597,190	The Netherlands	Pain and inflammation	Administrative data	MPR
Vincze et al.[164]	Retrospective cohort	11,187	United States	Hypertension	Administrative data	1 MPR 2 Length of therapy
Vranceanu et al.[165]	Randomized controlled trial	156	United States	HIV/AIDS	Self-report Electronically monitored	1 Questionnaire 2 MEMS
Vyavaharkar et al.[166]	Cross-sectional	224	United States	HIV/AIDS	Self-report	1 Missed dose 2 Modified Adult AIDS Clinical Trials Group Adherence Baseline Questionnaire
Wang et al.[167]	Retrospective cohort	896	Taiwan	Hypertension	Pharmacy claims data	1 MPR 2 MPR categories
Warden et al.[168]	Randomized controlled trial	567	United States	Depression	Self-report	Adherence questionnaire
Wei et al.[169]	Cross-sectional	7,583	United States	Parkinson disease	Administrative data	1 MPR 2 MPR categories 3 Persistence 4 Persistence dichotomy
Weizman et al.[170]	Prospective cohort	380	Canada	Inflammatory bowel disease	Self-report	MMAS-4
Whetten et al.[171]	Prospective cohort	468	Tanzania	HIV/AIDS	Self-report	1 Adult AIDS Clinical Trials Group Adherence Baseline Questionnaire 2 VAS
Wilke et al.[172]	Prospective cohort	1,517	Germany	Hypertension, diabetes, rheumatism, and asthma/allergy	Self-report	1 MMAS-4 2 MMAS-8
Williams et al.[173]	Prospective cohort	2,088	United States	HIV/AIDS	Self-report	Missed doses
Williams et al.[174]	Prospective cohort	96	West Indies	HIV/AIDS	Self-report	Questionnaire
Wu et al.[175]	Retrospective cohort	29,685	Taiwan	Hypertension	Administrative data	1 PDC 2 PDC threshold
Wutoh et al.[176]	Prospective cohort	100	United States	HIV/AIDS	Self-report	Structured interview
Xie et al.[177]	Retrospective cohort	17,465	United States	Hypertension	Administrative data	1 PDC 2 Discontinuation
Yoon and Ettner[178]	Retrospective cohort	83,893	United States	Hypertension	Administrative data	MPR
Yu et al.[179]	Retrospective cohort	2,496	United States	Overactive bladder	Administrative data	1 MPR 2 MPR categorized, time to discontinuation 3 Persistence rate
Yu et al.[180]	Retrospective cohort	23,494	United States	COPD	Administrative data	1 Treatment persistence 2 PDC 3 PDC threshold
Zeng et al.[181]	Retrospective cohort	4,525	United States	Hypertension	Administrative data	1 PDC 2 PDC threshold 3 Persistence
Zhu et al.[182]	Retrospective cohort	3,164	United States	Psoriatic arthritis	Administrative data	Time to discontinuation
Zyoud et al.[183]	Cross-sectional	410	Palestine	Hypertension	Self-report	MMAS-8

BMQ, Brief Medication Questionnaire; COPD, chronic obstructive pulmonary disease; CPCRA, Community Programs for Clinical Research on AIDS; Hb A_{1c}, glycated hemoglobin A_{1c}; MARS, Medication Adherence Rating Scale; MDD, major depressive disorder; MEMS, medication event monitoring system; MI, myocardial infarction; MMAS-4/8/9, Morisky 4-/8-/9-Item Medication Adherence Scale; MPR, medication possession ratio; PAM, Patient Adjustment to Medication; PDC, proportion of days covered; PMAQ, Patient Medication Adherence Questionnaire; RAMS, Reported Adherence to Medication Scale; VAS, visual analogue scale.

Table 3 – Methods and measures used to calculate adherence to multiple medications.

Adherence measurement methods per data collection method*	No. of studies, n (%)
Methods using prescription refill data/electronic medical records/pill counts/administrative claims/pharmacy claims data/patient's appointment records/other	77 (52.4)
PDC	26 (18.0)
MPR	23 (15.6)
Persistence rate	17 (11.6)
Time to discontinuation	7 (4.8)
Pill count	6 (4.1)
Medication gaps	3 (2.0)
Other methods for calculating medication adherence rate	24 (16.0)
Self-report methods	78 (53.1)
Multi-/single-item questionnaire or scales	72 (49.0)
Interview (telephone/face-to-face)	5 (3.4)
Missed doses	4 (2.7)
Daily diary	2 (1.4)
Informant rating (family member, nurse, or doctor)	1 (0.7)
Undefined (no further information given except self-report)	5 (3.4)
Clinical measures	16 (10.9)
HIV viral load	7 (4.8)
Blood pressure monitoring	3 (2.0)
$CD4^+$ cell count	2 (1.4)
Platelet aggregation	1 (0.7)
Hb A_{1c} level	1 (0.7)
Protease inhibitor level	1 (0.7)
Saliva concentrations of drug	1 (0.7)
Not reported clearly	3 (2.0)

$CD4^+$, cluster of differentiation 4; Hb A_{1c}, glycated hemoglobin A_{1c}; MPR, medication possession ratio; PDC, proportion of days covered.
* Please note that some studies included more than one method for measuring adherence to multiple medications.

Table 4 – Methods for measuring MMA in the included studies.

Calculation methods for adherence to multiple medications*	No. of studies, n (%)
MPR for multiple medications: In general, the numerator is the sum of days supplied for a medication (or combination of medications for MMA) and the denominator is the length of the study period. Most studies have at least one variant for either or both the numerator and the denominator	23 (15.6)
Average of ∑days of supply per medication/study period	4 (2.7)
∑days of supply for all medications/study period	4 (2.7)
∑days of supply for any medication/study period	2 (1.4)
Average of (∑days of supply/days between last prescription and first prescription) per medication; supply obtained in the last fill was excluded	2 (1.4)
Average of (∑days of supply/days between last prescription and first prescription) per medication	1 (0.7)
∑days of supply for multiple medications/(days between last prescription and first prescription + days of supply for last fill)	1 (0.7)
∑days of supply for all medications/(days between last prescription and first prescription + days of supply for last fill)	1 (0.7)
∑tablets dispensed/∑tablets recommended or prescribed	1 (0.7)
Weighted average of (∑days for supply/(days for which medication was needed − days spent in hospital)) per medication	1 (0.7)
Unclear how MPR to multiple medications was calculated	6 (4.1)
PDC: In general, the numerator is the sum of days covered by a medication (or combination of medications for MMA) and the denominator is the length of the study period. Most studies have at least one variant for either or both the numerator and denominator	26 (17.7)
Overlap variant (PDC overlap): The numerator counts only those days on which more than one drug/all drugs were available/accessible/prescribed or otherwise overlapping	12 (8.2)
∑days covered for all medications/study period	10 (6.8)
∑days covered for at least a given number of medications/study period	1 (0.7)
∑number of days the patient was prescribed index combination therapy/study period	1 (0.7)
Any drug variant PDC: The numerator includes days covered for any of the polytherapy combinations	2 (1.4)
The smallest number of days covered by any index medication/study period	1 (0.7)

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Table 4 – *continued*

Calculation methods for adherence to multiple medications*	No. of studies, n (%)
∑(Number of days for which a medication was available/study period or occurrence of 120-d medication gap)/number of medications	1 (0.7)
PDC described as MPR (PDC as MPR): The numerator stated it was the summation of days supplied and not days covered	11 (7.5)
Average of ∑days supplied per medication/study period	4 (2.7)
∑days supplied for all medications/study period	3 (2.0)
Average of (∑days supplied/(days between last prescription and first prescription + days supplied for the last fill)) per medication	2 (1.4)
∑days supplied for all medications/(study period − days of hospitalization)	1 (0.7)
∑days supplied for any medication/study period	1 (0.7)
Unclear how PDC to multiple medications was calculated	1 (0.7)
Missing days/doses for multiple medications	5 (3.4)
∑days without medications/study period	3 (2.0)
∑days without medications/days between last prescription and first prescription	1 (0.7)
(1 − ∑doses of medications/∑expected doses of medications) × 100	1 (0.7)
Other calculation methods for adherence to multiple medications	24 (16.3)
∑doses taken/∑doses prescribed over study period	6 (4.1)
Composite adherence score = a hierarchical algorithm that combines adherence data from medication event monitoring system, pill count, and self-report	3 (2.0)
∑days supplied for all medications/study period (not defined as MPR/PDC)	2 (1.4)
Continuous multiple-interval measures of medication availability = the sum of all the days' supply of medication/the number of days between the first fill and the last refill; the theoretical day's supply was calculated by dividing the number of units dispensed by the daily dose for the drug considered; the daily dose is the recommended dose per day for its main indication in adults	1 (0.7)
Covered minutes per day = [(1440 min − uncovered minutes)/1440 min] × 100	1 (0.7)
Daily patient possession ratio = look at each day in the observation period separately; determine how many medications are available, set a score between 0 (no medication available) and 1 (all medications available) weighted by the number of medications to be taken each day, resulting in daily scores indicating the proportion of medications available for each day; sum the scores and divide by the number of days in the observation period to obtain the proportion of all medications available for daily use	1 (0.7)
Medication total = ∑supply of pills dispensed/number of days elapsed	1 (0.7)
Overall pill count adherence score represented the mean pill count adherence across all prescribed medications	1 (0.7)
Proportion of medications taken during the past week	1 (0.7)
(Number of medications taken/number of medications prescribed) × 100 over a 7-d period	1 (0.7)
∑days pills taken/∑potential medications	1 (0.7)
Number of refills obtained over the prescribed number	1 (0.7)
∑days supplied for at least one medication/study period (not defined as MPR/PDC)	1 (0.7)
∑doses taken within ±3 h of the median time/∑doses prescribed over study period	1 (0.7)
Unclear how adherence to multiple medications was calculated	2 (1.4)
Self-reported measures	
MMAS	21 (14.3)
MMAS 4-item	15 (10.2)
MMAS 8-item	6 (4.1)
MMAS 9-item	1 (0.7)
Interview (telephone/face-to-face)	9 (6.1)
Questionnaire (unnamed, no further details)	7 (4.8)
Adult AIDS Clinical Trial Group Adherence to Combination Therapy Guide (also includes modified version)	6 (4.1)
Visual analogue scale	5 (3.4)
Informant rating (family member, nurse, or doctor)	5 (3.4)
Medication Adherence Rating Scale	4 (2.7)
Community Programs for Clinical Research on AIDS adherence form	4 (2.7)
Amount of medication consumed/taken (includes %)	4 (2.7)
Single item	3 (2.0)
Patient Medication Adherence Questionnaire (also includes revised version)	3 (2.0)
Reported Adherence to Medication Scale	3 (2.0)
Likert scale (five-point)	3 (2.0)
% missed doses of medication	3 (2.0)
Daily diary	2 (1.4)
Swedish HIV Cohort Study—Adherence Questionnaire	2 (1.4)
Adherence questionnaire	1 (0.7)
Basel Assessment of Adherence Scale for Immunosuppressives	1 (0.7)
Brief Medication Questionnaire	1 (0.7)

continued on next page

Table 4 – *continued*

Calculation methods for adherence to multiple medications*	No. of studies, n (%)
Immunosuppressant Therapy Adherence Scale	1 (0.7)
Medication Adherence Form	1 (0.7)
Medication Adherence Training Instrument	1 (0.7)
Medical Outcomes Study Specific Adherence Scale	1 (0.7)
Patient Adjustment to Medication	1 (0.7)
Summary of Diabetes Self-Care Activities	1 (0.7)
Treatment Regimen Adherence Questionnaire	1 (0.7)
Tablet Routines Questionnaire	1 (0.7)
Duke Severity of Illness Checklist	1 (0.7)
Undefined (no further information given except self-report)	2 (1.4)

MMA, multiple medication adherence; MMAS, Morisky Medication Adherence Scale; MPR, medication possession ratio; PDC, proportion of days covered.
* Please note that some studies included more than one method for measuring adherence to multiple medications.

supply even for monopharmacotherapy. Even though PDC includes an adjustment for overlapping days' supply of medication, it ignores the situations of early filling of prescriptions and stockpiling. Self-reported methods have been reported to overestimate adherence as compared with other measurement methods and possess less sensitivity. Follow-up simulation as well as validation studies that compare the performance of these MMA methods need to be conducted. Third, our review relied on what was reported by the authors, even though the terms they associated with their metrics may be inconsistent with more recently standardized definitions for the same terms and methods.

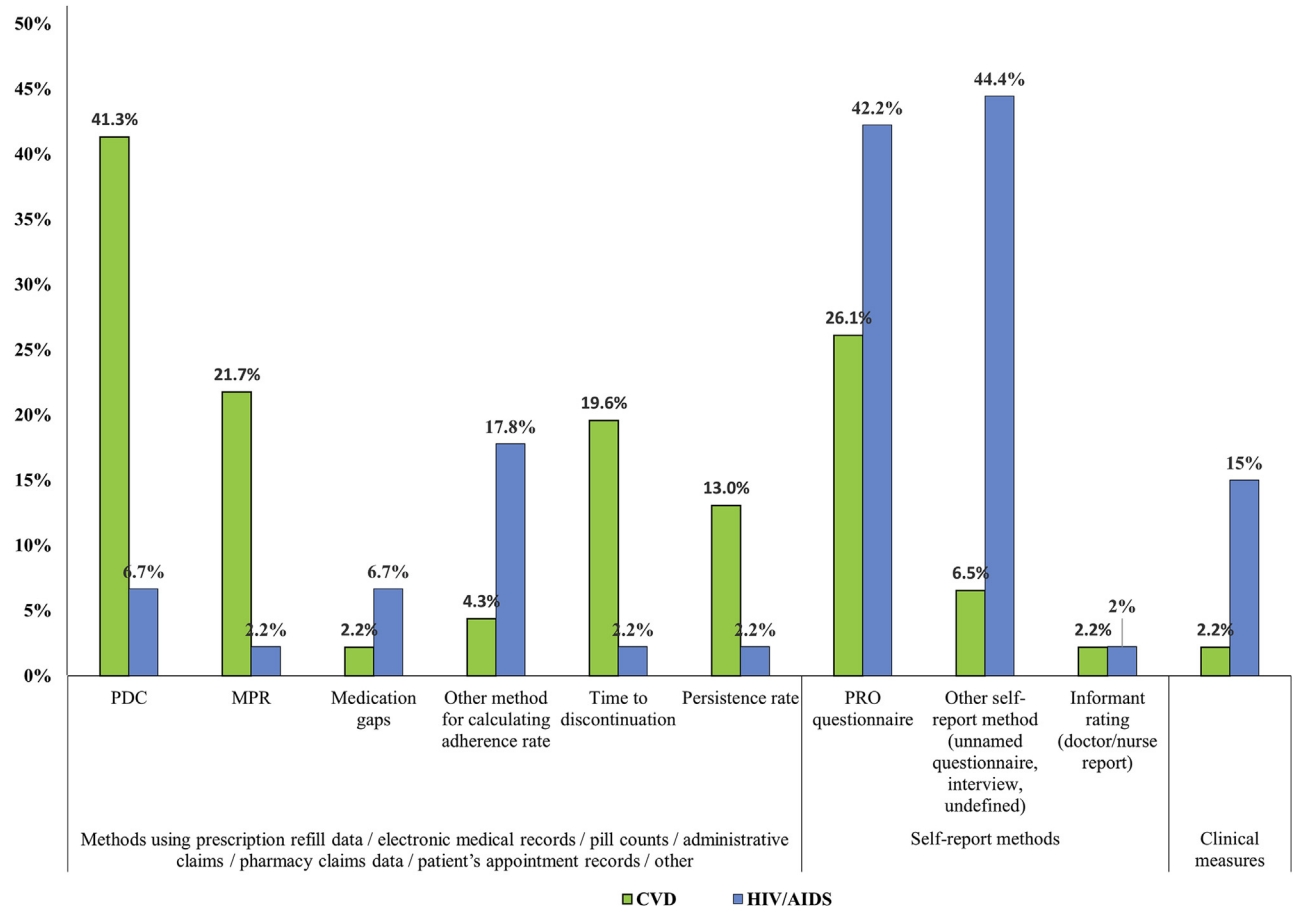

Fig. 2 – Measures used in the included studies assessing adherence to multiple medications in subjects with CVD or HIV/AIDS. CVD, cardiovascular disorder; MPR, medication possession ratio; PDC, proportion of days covered; PRO, patient-reported outcome.

For instance, in more than half the studies identified as using PDC, authors described the PDC numerator as the summation of days' supply when, operationally, only MPR is the summation of days' supply and PDC is the summation of days covered. Overlooking this subtle distinction between methods means the terms were misapplied or the terms had not been standardized at the time of publication or the authors did not differentiate the subtle differences. Similarly, most of the MMA studies seemed to require at least two fills for the medications under consideration. This is not a requirement for the measure, but rather a variant that potentially misses nonadherence among patients who stop taking the medication after their first fill.[33,41,42] Fourth, although we searched five large databases for relevant articles, our selection of search terms may not be exhaustive enough to rule out the possibility of missing studies despite reference mining. Fifth, the study inclusion/exclusion criteria did not require assessment of the quality of studies, which might have resulted in inclusion of studies with poor research methodology marked by high risks of bias, and concerns about the measures used. Finally, this review may have missed publications from last 2 years. Further research may evaluate the relationship between number of medications and adherence rate and the differences in medication adherence rate between medications that treat symptoms and those whose effects are not necessarily apparent to patients.

Conclusions

Our findings suggest that there is no criterion standard available to measure MMA. Furthermore, there is a lack of agreement between researchers on how to use a specific existing measure to calculate MMA. The choice of an appropriate method or a combination of methods was found to depend on the study setting, availability of data and other resources, and disease type. With increasing burden of comorbidities and prevalence of polypharmacy, more efforts should be directed toward constructing robust measures that can be used to evaluate adherence to complex regimens. This review also demonstrates that the researchers should undertake endeavors to formulate clear operationalization of MMA for a single disease as well as multiple diseases. Furthermore, it would be beneficial for future researchers to use multiple instruments simultaneously to validate MMA from various perspectives (e.g., self-report and administrative databases). And finally, the need for further research to understand the validity and reliability of all existing measures to evaluate MMA and their effects on objective clinical outcomes is paramount.

Acknowledgments

We extend special thanks to Theresa Tesoro at ISPOR—the professional society for health economics and outcomes research, and the librarian of the University of the Sciences for their support.

Source of financial support: The authors have no other financial relationships to disclose.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.08.006.

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