Abstract

Background: Medication non-adherence of patients with chronic conditions is a complex phenomenon contributing to increased economic burden and decreased quality of life. Intervention development relies on accurately assessing adherence but no 'gold standard' method currently exists. **Purpose:** The present scoping review aimed to: a) review and describe current methods of assessing medication adherence (MA) in patients with chronic conditions with the highest non-adherence rates (asthma, cancer, diabetes, epilepsy, HIV/AIDS, hypertension), b) outline and compare the evidence on the quality indicators between assessment methods (e.g., sensitivity), and c) provide evidence-based recommendations. **Methods:** PubMed, PsycINFO and Scopus databases were screened, resulting in 62,592 studies of which 71 met criteria and were included. **Results:** Twenty-seven self-report and ten non-self-report measures were identified. The Medication Adherence Report Scale (MARS-5) was found to be the most accurate self-report, whereas electronic monitoring devices such as Medication Event Monitoring System (MEMS) corresponded to the most accurate non-self-report. Higher MA rates were reported when assessed using self-reports compared to non-self-reports, except from pill counts. **Conclusions:** Professionals are advised to use a combination of self-report (like MARS-5) and non-self-report measures (like MEMS) as these were found to be the most accurate and reliable measures. This is the first review examining self and non-self-report methods for MA, across chronic conditions with the highest non-adherence rates and provides evidence-based recommendations. It highlights that MA assessment methods are understudied in certain conditions, like epilepsy. Before selecting a MA measure,

professionals are advised to inspect its quality indicators. Feasibility of measures should be explored in future studies as there is presently a lack of evidence.

Keywords: Medication Adherence; Assessment; Self-reports; Chronic Conditions; Scoping Review

Introduction

According to the World Health Organization (WHO), chronic conditions are defined as long duration or persistent illnesses with generally slow progression [1,2]. Medication non-adherence (MNA) constitutes a serious problem for patients with chronic conditions and especially for patients with comorbid chronic conditions. It results in considerable symptom burden, greater decline in health outcomes including quality of life, increased mortality, hospitalizations and healthcare costs [1,3–5]. Medication adherence (MA) refers to the extent to which patients take their medication(s) as recommended by their healthcare provider [1,4,5]. MA is comprised of *initiation*, which refers to when the patient takes their first dose; *implementation* of the dosing regimen, which refers to the correspondence of the actual dose to the prescribed; and *discontinuation* of treatment, which refers to treatment termination before the indicated timeframe or omission of the next dose(s) [6]. Thus, MNA occurs when the patient demonstrates either non-initiation of medication, suboptimal implementation or premature discontinuation of the treatment [6]. Based on WHO and other literature [1,7,8], chronic conditions that present with the highest rates of MNA include asthma, cancer, diabetes, epilepsy, HIV/AIDS, and hypertension.

Several studies report the development and implementation of interventions aiming to improve MA across the chronic conditions with the highest MNA rates [9–11]. However, interventions can only be effective if MNA is correctly identified and validly measured. Also, recommendations given by clinicians and decisions to change medications depend on reliable MA measurement. Therefore, reliable MA measurement can lead to more effective MNA-combating interventions with the potential to improve patients' health outcomes while reducing healthcare expenditures. Currently, a wide variety of measures exists [5,12,13] for assessing MA

in patients with health conditions (e.g., diabetes, glaucoma, tuberculosis, obesity), with "no gold standard" method to assess MA identified.

Self-report methods of assessing MA require patients evaluating and reporting their adherence for a certain time-period (e.g., the previous two weeks) [14,15]. They are the most prevalent assessment methods as they are inexpensive, easy and quick to administer [5,13–15]. Examples of self-reports include interviews with patients and questionnaires [14,15]. Some of the most widely used self-report measures for MA include: the Morisky Medication Adherence Scale (MMAS-8) [16] and the Medication Adherence Report Scale (MARS-5) [17]. Non-self-report methods are less frequently used and include more objective measures of MA [5,18]. Key advantages of non-self-reports are increased reliability compared to self-reports, and easy quantification of results [19]. Non-self-reports include pill counts, electronic monitoring systems, and biological biomarkers [14,20,21]. Evaluation of MA with biological biomarkers is usually made through blood or urine tests to examine if prescribed medication was consumed as indicated [14,20]. Nowadays, electronic monitoring systems are increasingly used with the most commonly and widely used device among chronic patient groups being the Medication Event Monitoring System (MEMS) [22].

Mixed findings on accuracy, reliability and validity of existing MA self-report assessments are observed in patients with health conditions such as cystic fibrosis, HIV and glaucoma [5,12,13]. Self-report measures, particularly questionnaires and diaries, have moderate to high correlations with non-self-reports [5,13], while self-reports and pill counts tended to overestimate MA compared to MEMS [12]. Possible misperceptions or the inclination of people to provide socially acceptable responses might explain the MA overestimation in self-reports and pill counts [21,23]. There appears to be a tendency in the literature to evaluate MA methods

irrespective of condition and whether these present with high rates of MNA [5,12,13]. The type of chronic condition is an important factor to consider when assessing MA, as different conditions such as psychiatric, may present with different symptomatology or reasons for MNA which can thus impact upon sensitivity of assessment methods and their ability to capture adherence in the specific conditions of interest. Also, we can learn more by focusing on conditions with high MNA. Moreover, there is a need to examine the accuracy of MA assessment methods. Accuracy refers to the closeness of a measurement to the reference (e.g., self-reports vs. MEMS) [24] as examined with clinical relevance indicators like sensitivity and specificity, in order for them to be utilized by clinicians and researchers in their daily practice.

The Present Study

This scoping review aimed to collate evidence on measurement properties of MA methods for patients that according to WHO [1] present with the highest prevalence of MNA across chronic conditions: asthma, cancer, diabetes, epilepsy, HIV/AIDS, and hypertension. Further, it aimed to utilize the reviewed information to provide recommendations about MA methods for both researchers and clinicians. The main objectives were to: a) Review and describe the current methods of assessing MA; b) Outline and compare the evidence on the quality indicators of the self-report and non-self-report methods including, internal consistency, sensitivity, specificity, feasibility, convergent validity, and test-retest reliability; and c) Provide evidence-based recommendations for researchers and practitioners. This is the first review examining MA methods across chronic conditions that present with the highest MNA rates, and utilizes the information to provide recommendations for improvements in MA assessment to researchers and clinicians.

Methods

The scoping review was registered with PROSPERO (registration number: CRD42019134371). PRISMA guidelines for scoping reviews [25] were followed for reporting the review process. The data that support the findings of this study are available in Open Science Framework (OSF), reference number (10.17605/OSF.IO/B3XE7).

Eligibility criteria

Published studies of adults, diagnosed with one of, or a combination of, the following chronic conditions: asthma, cancer, diabetes, epilepsy, HIV/AIDS, and hypertension, were eligible for selection. Eligible studies had to describe the development and/or use of a self-report or a non-self-report method for assessing MA and report values for at least one of the following quality indicators: internal consistency, sensitivity, specificity, feasibility, test-retest reliability, or convergent validity/agreement between self-reports and non-self-reports. Observational studies (including cross-sectional, prospective, and retrospective) and randomized controlled trials were included. Studies were excluded if: a) published in a language other than English; b) were letters, reviews, editorials, conference abstracts, case or qualitative studies; and c) examined MA of patients with psychiatric disorders or a comorbid chronic condition with psychiatric disorders.

Search Strategy, Study Selection and Synthesis

Relevant studies were identified by searching the databases of PubMed, PsycINFO and Scopus. No date restriction was used in the search. Existent meta-analyses and reviews were hand-searched for additional potentially eligible studies. Appendix A presents the search terms and strategy, and Appendix B the included studies. Papers were screened for eligibility at title/abstract and full-text screening stages by two authors independently, with crosschecking

between them. Inter-rater reliability (IRR) between the two authors was calculated using Cohen's kappa [26]. An almost perfect agreement was observed during title/abstract screening (*IRR*=93%; *k*=.85) and for the full-text screening stage (*IRR*=98%; *k*=.95). Any discrepancies were resolved in research team consensus meetings. A narrative synthesis [27,28] was used to collate the extracted evidence, particularly for describing studies' characteristics, participants' MA, and assessment of MA across the six chronic conditions of interest.

Data Extraction and Analysis

A data charting form in Microsoft Excel was used to extract the data (see Appendix C). The Mean (M) and Standard Deviation (SD) of the proportion of participants adhering to medication were computed. The following quality indicators were extracted:

Internal consistency was reported only for self-reports, defined as the agreement between several items of a particular method to measure a given construct. It was assessed using Cronbach's alpha coefficient where >.70 was considered acceptable [29].

Feasibility was reported as percentage of acceptability, perceived usefulness, and satisfaction provided by study participants for a particular assessment measure [30]. Higher percentages indicate higher satisfaction or acceptability.

Clinical relevance was reported using the sensitivity and specificity percentages, and the positive and negative predictive values (PPV and NPV respectively). Sensitivity was defined as the proportion of individuals who were adherent to medication, being correctly identified by the measure (PPV probability indicator) [31]. Specificity was defined as the proportion of people who were non-adherent, being correctly identified by the particular measure (NPV probability indicator) [31]. High sensitivity and specificity of 80-100% represented the ability of the assessment measure to correctly identify MA and MNA, with minimal false positives and false

negatives respectively [31,32]. In the case of studies that did not report positive and negative predictive values but instead reported true and false positives and negatives, the indicators were computed using formulas (see Appendix D).

Convergent validity was reported as the correlation between two methods measuring the same construct [33]; reported using Pearson's or Spearman's correlation coefficients, with those greater than .80 indicating high correlation, .40-.80 indicating moderate, and <.40 indicating low correlation [13,33].

Test-retest reliability was defined as stability of a measure over time [34], reported using Pearson's or Spearman's correlation coefficients between two different time points. Coefficients greater than .90 indicate high reliability, coefficients .80-.90 indicate moderate, and coefficients <.80 insufficient reliability [34].

Agreement/correlation between methods was defined as the concordance between self-report and non-self-report measures for assessing MA [13,35], was reported using Cohen's kappa or Pearson's or Spearman's correlation coefficient. Kappa coefficients >.60 indicate high agreement, coefficients .40-.60 moderate, and coefficients <.40 low agreement [13,35]. Pearson's or Spearman's correlation coefficients greater than .80 indicate high correlation between measures.

Results

Study Characteristics

A total of 62,592 studies were identified. After removing duplicates and screening the titles, the abstracts of 118 records were screened and 71 retained (Figure 1). The full-text of 16 studies (seven in hypertension, three in HIV, two in asthma, two in diabetes, one in cancer, and one in comorbid conditions) could not be accessed even after contacting corresponding authors

and were excluded. The characteristics of the 71 included studies are presented in Table 1. These were published between 1988 and 2020, with the majority conducted in the USA (*n*=24, 33.8%) and European countries (*n*=21, 29.6%), followed by Asian countries (*n*=13, 18.3%), UK (*n*=6, 8.5%), Africa (*n*=3, 4.2%), Canada (*n*=3, 4.2%) and Brazil (*n*=1, 1.4%). Thirty-five (49.3%) assessed MA using only self-reports, four (5.6%) using only non-self-reports, and 32 (45.1%) compared self-report with non-self-report methods. Most studies implemented a cross-sectional research design (*n*=46, 64.8%) with only ten studies assessing MA in clinical trials (14.1%). The majority assessed MA in patients with hypertension (*n*=33, 46.5%) and diabetes (*n*=18, 25.4%), followed by cancer (*n*=7, 9.9%), HIV/AIDS (*n*=5, 7.0%), asthma (*n*=5, 7.0%), a combination of these chronic conditions (e.g., diabetes and hypertension; *n*=2, 2.8%), and epilepsy (*n*=1, 1.4%). The MA rates reported for each condition are presented in Online Supl. Table 1. A summary of findings and an overview of the performance of each measure is provided in Table 2.

Self-report Methods

Twenty-seven different self-report measures were used to assess MA, with most being questionnaires (*n*=21/27, 77.8%) followed by questions or scales developed or adapted specifically for the particular study (*n*=6/27, 22.2%). Ten (37.0%) self-report measures were developed to assess MA across various conditions, whereas 17 (63.0%) were condition-specific measures. Condition-specific measures assessed adherence to specific medications such as antihypertensives, with some studies either developing (e.g., Hill-Bone Compliance to High Blood Pressure Therapy Scale (HCBS)) or adopting existing validated measures (e.g., Medication Adherence Report Scale for Asthma (MARS-A). In contrast, non-condition-specific measures assessed adherence generally with most studies administering already existing and previously used questionnaires (e.g., MMAS-8, MARS-5). In terms of quality indicators, internal

consistency was reported for 18 of the measures (66.7%), convergent validity for 23 (85.2%), and test-retest reliability for eight measures (29.6%). Sensitivity and specificity were reported for 17 measures (63.0%), whereas positive and negative predictive values for 14 (51.9%). Feasibility was not reported for any measure. Findings per each measure are presented in Online Supl. Table 2 and a summary of findings in Table 2 including the number of studies used to assess each quality indicator.

Non-condition-specific measures. The most frequent measure used across conditions utilizing only MA self-reports (*n*=35) or both methods (*n*=32) was MMAS-8 [16] (*n*=18/67, 29.9%), followed by researcher-developed questions on doses taken/missed in a specified time period (e.g., one week; *n*=15/67, 22.4%). Ten studies (14.9%) used the Morisky Green Levine Medication Adherence Scale (MGLS) [36] and eight studies (11.9%) used the MARS-5 [17]. The rest of the measures (*n*=5, 50.0%) were utilized only by one or two studies.

The majority of studies (*n*=25 out of 29 reporting values; 86.2%) showed low internal consistency (<.70), insufficient test-retest reliability (<.80), and low clinical relevance (sensitivity, specificity, positive and negative predictive values <80%) for MMAS-8, MGLS, and researcher-developed questions on doses taken/missed. For example, for MMAS-8, internal consistency ranged from .47 to .81 (*M*=.64), whereas for MGLS sensitivity ranged from 32-74% (*M*=50%), and for researcher-developed questions test-retest reliability ranged from .45-.56 (*M*=.51). Additionally, mixed findings were observed on convergent validity with some studies supporting high correlation ($r \geq .80$) between measures (e.g., MMAS-8 with MGLS), whereas others showed moderate correlation ($r = .40$-$.80$) between for example MGLS with MARS-5 or low correlation ($r \leq .40$) between researcher-developed questions with MGLS.

Studies using MARS-5, reported acceptable internal consistency (*M*=.77; Cronbach's *alpha* range: .70-.82), high test-retest reliability (*r*=.97), and high specificity (*M*=94; range: 90-97%; Table 2). Also, its sensitivity and positive predictive value were <80%, whereas mixed findings on convergent validity were observed, with most correlations (range *r*=.27-.67) being moderate (e.g., with pill counts) or low (e.g., with pharmacy refills). Convergent validity of the measures utilized by one/two studies was found to be moderate or low.

Condition-specific measures. Most of the self-report measures (*n*=17/27, 63.0%) were developed to assess MA for specific conditions. For hypertension, there were eight measures with the HCBS used in most studies (*n*=4/67, 6.0%), which along with the Medication Adherence Self-Efficacy Scale-Revised (MASE-R; *n*=1, 1.5%) showed acceptable internal consistency (>.70). Only the Adherence Self-report Questionnaire (ASRQ; *n*=1, 1.5%) had high negative predictive value (84%) and convergent validity (MEMS: *k*=.73). For diabetes, three measures were identified, with the Iraqi Anti-Diabetic Medication Adherence Scale (IADMAS; *n*=1, 1.5%) showing acceptable internal consistency (Cronbach's *alpha*=.71), excellent test-retest reliability (*r*=.81), high sensitivity (100%), and negative predictive value (100%). For HIV/AIDS, there were two measures, with only AIDS Clinical Trials Group questionnaire (ACTG; *n*=3, 4.5%) showing high specificity (85%). For asthma, there were two measures with MARS-A (*n*=2, 3.0%) having acceptable internal consistency (*M*=.85; Cronbach's *alpha* range: .73-.85) and high sensitivity (82%). For cancer, only the Medication Assessment Tool for Cancer Pain (MAT-CP *n*=2, 3.0%) was reported, showing high test-retest reliability (*M*=.89; range *k*=.86-.92). For epilepsy, no measures were identified.

Summary. Overall, numerous condition-specific and non-specific measures exist with high variability observed on the values of quality indicators. Across non-specific measures,

MARS-5 and ARMS showed the best psychometric properties whereas IADMAS (for diabetes), MARS-A (for asthma) and ASRQ (for hypertension) showed the best properties across condition-specific measures.

Non-self-report Methods

Ten non-self-report measures were identified, presenting with similar operationalization of the key constructs (e.g., pill count was operationalized as counting the number of pills dispensed from the container, across all studies). Such measures included for example pharmacy refills/records, which assessed adherence as whether prescribed medication was refilled from pharmacies. Electronic monitoring devices including MEMS, MedSignals pillbox, eCAP and Adjusted Electronic Monitored Dose (AEMD) monitored MA by recording the date and time that the bottle or pillbox was opened and closed. Another electronic monitoring device included the Metered-Dose Inhaler (MDI) log monitor that was used in asthma to record date and time of using an MDI. E-prescription programs prescribe medications electronically and MA was assessed by the transmission of prescription to a patient-preferred pharmacy. MA biochemical analysis, involves assessing medication presence via biological biomarkers, such as plasma concentrations and urinary potassium excretion levels. Finally, physician claims from clinical records were also used.

In terms of quality indicators, convergent validity was reported for eight measures (80.0%), sensitivity and specificity for six (60.0%), positive and negative predictive values for four (40.0%) and feasibility only for one measure (10.0%). Pharmacy refills/records (*n*=9, 25.0%) and MEMS (*n*=9, 25.0%) were the most prevalent in studies assessing MA, either alone (*n*=4) or combined with self-reports (*n*=32); followed by pill counts (*n*=7, 19.4%) and

biochemical analysis (*n*=3, 8.3%). A summary of findings is presented in Table 2 and specific findings per each non-self-report measure in Online Supl. Table 3.

Overall, across conditions, electronic monitoring methods showed the highest values in quality indicators. MEMS showed high specificity (83.0%) and positive predictive value (93.0%) and low-to-high convergent validity (range *r*=-.29-.73). AEMD [37] also showed high values on clinical relevance indicators such as sensitivity, feasibility (91.0% of participants reporting high acceptability of the measure) and moderate convergent validity with pill counts (*r*=.70). Additionally, e-prescription programs [38] showed high specificity (92.0%) and negative predictive values (90.0%), whereas MedSignals pillbox [39] showed high specificity (98.0%). Convergent validity of e-prescription programs and MedSignals pillbox was not reported. Further, pharmacy refills showed only high positive predictive value (96%) whereas pill counts showed only high convergent validity (e.g., with AEMD: *r*=.91).

Summary. Overall, electronic monitoring devices including AEMD, MEMS and e-prescription programs showed the best psychometric properties, whereas pill count and pharmacy refills the lowest.

Comparing Self-report with Non-self-report methods

MA rates tended to be higher when using self-reports than non-self-reports, except for pill counts (Online Supl. Table 4). In particular, when using pill counts MA was higher (*M*=75.9, *SD*=18.3) compared to self-reports (*M*=69.8, *SD*=22.5) in six studies comparing them (18.8%). In studies comparing self-reports with MEMS (*n*=11/32, 34.4%), MA varied from 57-88% (*M*=73.5, *SD*=13.2) for MEMS, whilst for self-reports it varied from 72-91% (*M*=84.8, *SD*=6.0). For physician claim/reports (*n*=5/32, 15.6%), MA varied from 59-95% (*M*=76.4, *SD*=16.5), whereas for self-reports it varied from 83-92% (*M*=86.9, *SD*=4.0). MA was also higher in self-

reports (*n*=4, 12.5%; *M*=54.9, *SD*=26.5) compared to other electronic devices (*M*=46.4, *SD*=19.1). For pharmacy refills and biochemical analysis, the difference with self-reports in terms of MA rates was small. Specifically, for pharmacy refills (*n*=13, 40.6%), MA varied from 41-91% (*M*=71.9, *SD*=17.3) whereas for self-reports varied from 24-94% (*M*=71.7, *SD*=20.6). Regarding biochemical analysis (*n*=3, 9.4%), MA varied from 62-98% (*M*=78.1, *SD*=18.4) compared to self-reports which varied from 61-88% (*M*=77.1, *SD*=14.0).

Most of the studies used different thresholds in self-reports vs. non-self-reports on determining MA (see Online Supl. Table 4). For example, in studies comparing pill counts with self-reports, most of them used as MA threshold in pill counts as having taken medication equally or higher than 80% (e.g., [40–42]) compared to self-reports in which the threshold was determined mostly based on the total score (e.g., MMAS-8: high MA=8, medium=6-7, low<6) [43]. Another example includes studies comparing MEMS with self-report measures, with some using as MA threshold in MEMS having taken medication equally or higher than 80% (e.g., [44,45]) whereas others used the total percentage of doses taken (e.g., [46–48]). In contrast, in the self-reports either the same threshold as non-self-reports was used (e.g., [44,46,47]) or categorized participants as adherent or not based on their score (e.g., adherent: negative responses to all questions) [48].

High agreement (see Table 2) was observed only between MEMS and the ASRQ (*k*=.73) [45] and between pill counts and researcher-developed questions (*k*=.76) [42], pill counts and MARS-5 (*k*=.74) [42], and pill counts and interview questions (*k*=.65) [40]. Moderate correlation was reported between the MDI-log monitor and MARS-A (*r*=.42). Mixed findings were observed when comparing MMAS-8 with pharmacy refills, biochemical analysis and pill counts,

with high (range *k*=.75-.84) and moderate (range *r*=.63-.73) agreement observed in two studies [49,50], and low and no significant agreement in two others [43,51].

Summary. Overall, great variability on the agreement between self-reports and non-self-reports was observed with most of the values being moderate or low, suggesting a difference between MA assessment methods.

Quality Indicators of Measures between Chronic Conditions

Some measures performed better than others for specific conditions. Regarding self-reports, one study [52] reported that MMAS-8 showed acceptable internal consistency (Cronbach's *alpha*=.70) and high sensitivity (80.0%), specificity (89.0%), positive (84.0%) and negative (86.0%) predictive values when used in comorbid conditions (i.e., diabetes and hypertension; see Online Supl. Table 2). Further, MEMS and pharmacy refills were used more often in patients with hypertension, showing high values on clinical relevance indicators (see Online Supl. Table 3). Also, in patients with hypertension, developed questions, ASRQ and MARS-5 showed high agreement with MEMS and pill counts (e.g., [42,45]), whereas for the rest of the conditions agreement/correlations were mostly moderate and low (Online Supl. Table 4).

Discussion

A total of 71 studies across patients with asthma, cancer, diabetes, epilepsy, HIV/AIDS, and hypertension were included in the review, with the majority assessing MA using only self-report methods. A range of measures were identified with 27 self-reports (17 condition-specific and 10 generic self-report) and 10 non-self-reports. Most measures showed low values in quality indicators such as sensitivity and specificity. The absence of general guidelines on MA assessment [5,12,13] might explain the development and existence of this large variability of measures. Together with our finding, there is a great need of providing evidence-based

recommendations on which measures should be used across and in specific chronic conditions to assess and ultimately be able to solve problems in MNA. Also, this review observed that MA assessment methods in certain chronic conditions, such as epilepsy are understudied. Complexity of assessing MA in patients with epilepsy perhaps contributes to dearth of measures for this condition. Detecting whether a patient adheres to antiepileptic medications is more costly, complex, and time-consuming than for other conditions as it requires more specialized measures, particularly blood plasma, hair, or saliva concentration analyses [20]. Absence of MA assessment methods for epilepsy leads to the design of ineffective interventions and thus poor outcomes and increased mortality [10]. Future studies should consider developing or adapting existing reliable MA measures to patients with epilepsy, whilst finding new ways to overcome difficulties precluding the measurement of MA in this condition.

Across conditions, MARS-5 [17] was the self-report measure with the best psychometric properties, showing high internal consistency, specificity, and test-retest reliability. MARS-5 is one of the most commonly and widely used cross-cultural questionnaires associated with good psychometric properties [53]. Additionally, we found that electronic monitoring devices were the most accurate non-self-report measures. In particular, clinical relevance indicators such as sensitivity and specificity suggest that MEMS, AEMD, e-prescription programs and MedSignals pillbox are more accurately assessing MA especially in patients with HIV/AIDS or hypertension [39,44], compared to other non-self-report measures like pill count and pharmacy refills. Noticeably, self-reports tend to indicate higher rates of MA compared to non-self-reports (with the exception of pill counts). The tendency of people to elicit socially acceptable responses, possible misperceptions regarding their medication intake, or memory recall difficulties might lead patients to over report adherence to medications [12,20,21,23]. Therefore, researchers and

clinicians interested in assessing MA are advised to use a multi-method approach with a combination of electronic monitoring methods and self-report measures. Whereas electronic methods are recommended in order to more accurately assess MA rates, self-report measures can provide a better understanding of adherence patterns, patients' medication-taking behavior, beliefs and possible barriers to MA, and to facilitate a more accurate understanding of the particular circumstances surrounding patients' medication regimen adherence [5,13,14]. Using a combination of reliable self-report and non-self-report measures might solve the problem of MA assessment as the combination can provide higher accuracy of assessing MA and result in stronger predictive power. Use of reliable, accurate and valid assessment MA methods can enable both researchers and clinicians to reach conclusions, identify factors that can aid MA, and implement targeted and effective interventions to combat MNA.

Similar to self-reports, pill counts tend to overestimate MA as they are functionally related to self-reports, in that individuals may engage in pill dumping or hoarding. Their assessment relies on entrusting patients to bring in their pills to the healthcare provider, which impacts their objectivity [12,15,21]. Not surprisingly, pill counts result in low sensitivity and specificity in assessing MA. Yet, pill count is a commonly used measure in clinical trials as it is considered a more objective means of MA assessment compared to self-reports [14]. Together with previous findings of pill counts' overestimation of MA [12,15,21], we suggest that researchers and clinicians be aware of the associated objectivity, sensitivity and specificity problems. They should thus either choose a different method of assessment or interpret findings with caution. However, some barriers including high cost preclude many researchers and clinicians from using more objective non-self-report measures, such as electronic monitoring devices [18]. The trade-off between lower-cost options and accuracy should be further explored.

Clinicians may need to initiate a dialogue with manufacturers for reducing prices or investigate financial support opportunities from insurance companies and healthcare systems. Further, pairing up of different professionals (e.g., IT experts and developers, researchers from different modalities) might help discover better and cheaper IT solutions. For example, use of applications in mobile devices from patients' own space appears to be an effective method for MA assessment [54] and such advancements can be expanded upon. Particularly useful can be an Ecological Momentary Assessment (EMA) approach involving multiple repeated assessments in natural environments via the use of mobile devices [55,56]. Researchers and clinicians can use EMA to examine MNA patterns and individualize MA assessment to match prescription regiments while allowing for information to be shared with the treating practitioner.

This scoping review also highlighted a number of issues related to the psychometric properties and choice of quality indicators. Surprisingly, almost half of included studies did not provide data on clinical relevance, such as sensitivity and specificity, and test-retest reliability, and instead reported only on internal consistency. This is not sufficient to determine stability and representativeness of MA over time. These are important issues that were previously raised [23] and have not yet been adequately addressed. Future studies need to utilize more rigorous methodologies and analyses when describing measure properties and ensure examination of quality indicators. Randomized-controlled trial methodologies or single-case design studies, employing rigorous statistical analyses, such as the Bland-Altman allowing for multi-method comparisons may be one solution. Bland-Altman analysis describes the agreement between measurements or instruments with the advantage of revealing both systematic and random errors [57]. These recommendations if adopted, will help future reviews and meta-analyses to reach more accurate conclusions for the assessment of MA.

Further, feasibility was examined in only two studies [30,39] suggesting that the view and feedback of patients is not generally considered. Researchers are strongly encouraged to explore and ensure the feasibility of measures utilizing user-centered approaches in their measure development and testing. A good and accurate measure is not only determined by its psychometric properties but also by its acceptability and usefulness as reported by the target population [5]. User-centered designs and patient-centered approaches might be particularly useful when developing assessment methods for MA, as patients are actively involved in decisions about their medication assessment, management and treatment, and they can present their needs, difficulties, and barriers [58]. All other stakeholders (e.g., healthcare providers) should also be included when deciding on methods to assess this problem so as to ensure that the measure produced will be used by the target group. Particularly in clinical practice, choice of assessment method should be undertaken collaboratively with patients and practitioners.

Interestingly, common use of certain measures does not necessarily imply their good psychometric properties. For example, MMAS-8 [16] and MGLS [36] were commonly used, however, they presented with low internal consistency, insufficient test-retest reliability, low clinical relevance values and mostly low correlation with non-self-reports. In combination with previous findings [5,53], it is advisable to select assessment tools based on the psychometric properties reported rather than their common usage. In addition, it was observed that the various self-report measures (e.g., MMAS-8, MGLS, HCBS) do not take into account medication frequency (daily vs. multiple times per day) and medication complexity (single vs. multiple medications for different conditions). Many studies also categorized MA based on the total score of the questionnaire (e.g., high vs. low MA) with the number of medications taken or missed not considered. MA is a complex process involving disruptions in initiation, implementation and

discontinuation of prescribed treatment [6], with the frequency, quantity and complexity need to be taken into account in self-report measures. Further, though some measures demonstrated good psychometric properties in assessing MA (e.g., ARMS [59], IADMAS [60], MARS-A [61] and MMAS-8 [52] for hypertension, diabetes, asthma and comorbid conditions respectively), the studies utilizing or evaluating these measures were too few to reach accurate conclusions. It was noted that for certain conditions (e.g., hypertension) there are numerous similar measures only utilized in single studies. These contribute to inconclusive results regarding the assessment of the MA phenomenon [53]. Researchers and clinicians are advised to further examine and utilize the measures that performed well on assessing MA instead of developing new ones, and drop the use of measures that appear to be problematic and fall short when their psychometric properties are examined.

Another important point of consideration when choosing a MA assessment method is the choice between self-report vs. non self-report and possibly more objective measures of assessment. Many factors need to be considered in deciding among the different possibilities including ease of administration, cost, and clinicians' available time. Factored into this decision should be that MA outcomes differ between self-report and non-self-report methods. Usually for self-reports (e.g., questionnaires), a dichotomous cut off score is used to delineate MA compared to non-self-reports where more continuous (e.g., % of medication doses taken) is used. This contributes to a difficulty in directly comparing the different methods and drawing accurate conclusions as to which method is better and under which conditions. We advise the utilization of measures providing similar outcomes for MA (preferably continuous for both measure types) for direct comparison purposes.

Limitations

Results of this review should be considered in light of limitations. Firstly, findings cannot be generalized to the assessment of MA for certain health conditions (e.g., epilepsy) given that only a small number of studies were identified and included. Secondly, 16 possibly eligible studies were not included in this review, as we were unable to access their full-text, even after contacting the corresponding authors. However, a large number of studies were included and we feel that we have covered the topic satisfactorily. Finally, this review was limited to studies published only in English, which although included studies conducted in non-English speaking countries, results in an inherent bias and discounting of possible variations in MA assessment methods utilized in various countries and health care systems.

Conclusions

Overall, we suggest that no measure can be used as the "gold standard", as various limitations exist in the literature and future researchers should consider our recommendations when conducting their studies. Some of the limitations of included studies are the high variability of measures possibly due to the absence of evidence-based recommendations and the limited use of many measures to assess MA by only one or two studies. Additionally, many studies did not provide data on clinical relevance indicators, such as sensitivity and specificity, feasibility and test-retest reliability, and instead provided data only on internal consistency which is not sufficient to determine acceptability, stability and representativeness over time. Considering the limitations of self-reports, we recommend that researchers and clinicians should use a combination of specific self-report measures (like MARS-5) and electronic monitoring devices (non-self-report) as these were found to be the most accurate and reliable measures of assessing

MA across patients with health conditions presenting with the highest MNA rates (i.e., asthma, cancer, diabetes, epilepsy, HIV/AIDS and hypertension).

Further, before utilizing a measure, researchers and clinicians should examine its reported quality indicators and decide appropriateness of use. This study identified a dearth of evidence when examining the feasibility of MA measures for certain conditions (e.g., epilepsy). Based on this review, we also recommend that future studies aim to fill these gaps by conducting multi-method comparisons of MA self-report and non-self-report methods, both within and between patients, and utilizing more rigorous and specialized statistical methods when comparing methods [62]. Our review is the first to examine both self-report and non-self-report methods in assessing MA across chronic conditions with the highest MNA rates, and provides recommendations for researchers and clinicians with an eye to improve MA and MNA assessment. Proper and accurate assessment of the phenomenon of MA and MNA will allow for more effective and targeted interventions to be developed to combat this significant public health problem [63].

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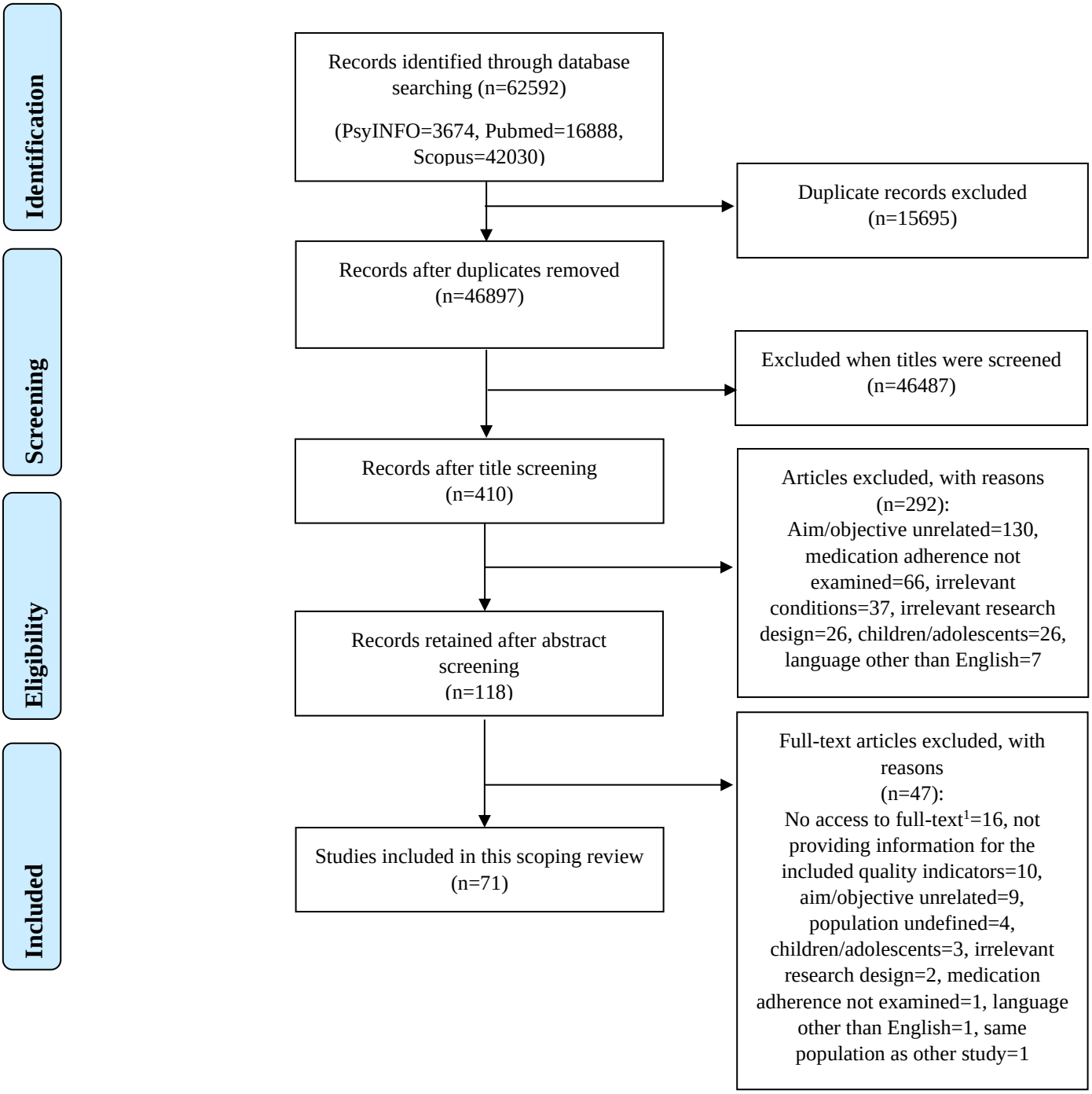
Figure captions

Figure 1. Flow diagram of information from identification to inclusion of studies in this review.

Note. [1]An attempt was made to get the full-text by conducting the corresponding author of the article, but failed.

Figure


Identification
Screening
Eligibility
Included
Records identified through database searching (n=62592)
(PsyINFO=3674, Pubmed=16888, Scopus=42030)
Duplicate records excluded (n=15695)
Records after duplicates removed (n=46897)
Excluded when titles were screened (n=46487)
Records after title screening (n=410)
Articles excluded, with reasons (n=292): Aim/objective unrelated=130, medication adherence not examined=66, irrelevant conditions=37, irrelevant research design=26, children/adolescents=26, language other than English=7
Records retained after abstract screening (n=118)
Full-text articles excluded, with reasons (n=47): No access to full-text[1]=16, not providing information for the included quality indicators=10, aim/objective unrelated=9, population undefined=4, children/adolescents=3, irrelevant research design=2, medication adherence not examined=1, language other than English=1, same population as other study=1
Studies included in this scoping review (n=71)

Tables

Table 1

Description of included studies (N=71)

Study[1]	Country	Type of Study[2]	Research Design	Sample Size	Age[3] (M, SD)	Gender (% females)	Medication[4]	MA measure of assessment[5]
Asthma (*n*=5)								
Cohen et al. (2009) [1]	USA	Health care	Prospective	53	47.0 (12.0)	85.0%	ICS	MARS-A, MDI-log monitor
Mora et al. (2011) [2]	USA	Health care	Prospective	294	48.0 (NR)	82.0%	ICS	MARS-A
Schatz et al. (2013) [3]	USA	Health care	Cross-sectional	420	41.6 (9.1)	66.7%	ICS	AAA-Q
Unni & Farris (2015) [4]	USA	Health care	Cross-sectional	840	48.7 (NR)	61.4%	AMM	MARS-5, MGLS
Van Steenis et al. (2014) [5]	Netherlands	Health care	Cross-sectional	93	43.7 (14.5)	59.1%	ICS	MGLS, PR
Cancer (*n*=7)								
Bright & Stanton (2019) [6]	USA	Health care	Prospective	112	54.0 (NR)	100%	ET	N of days forgot medications, MEMS
Font et al. (2012) [7]	Spain	Health care	Retrospective	692	NR	100%	ET	Physician report, Telephone question, ADRD
Håkonsen et al. (2006) [8]	Norway	Health care	Retrospective	109	60.8 (11.5)	47.7%	PD	MAT-CP
Håkonsen et al. (2008) [9]	UK	Health care	Retrospective	101	68.9 (13.5)	44.6%	CM	MAT-CP
Oberguggenberger et al. (2012) [10]	Austria	Health care	Cross-sectional	242	MDN=65.0 (8.3)	100%	ET	SMAQ, MARS-5, Physician report, PR, Plasma concentrations
Oldenmenger et al. (2007) [11]	Netherlands	Health care	Prospective	46	MDN=56.0 (NR)	56.0%	Analgesics	MEMS, Diary
Tzeng et al. (2008) [12]	Taiwan	Clinical trial	Cross-sectional	135	58.4 (15.6)	59.0%	Analgesics	MGLS
Diabetes (*n*=18)								
Ayoub et al. (2019) [13]	Lebanon	Health care	Cross-sectional	500	59.2 (10.7)	59.8%	OAM	DMAS
Chua et al. (2013) [14]	Malaysia	Clinical trial	RCT	84	MALMAS=61.9 (9.1) MMAS=64.7 (9.6)	NR	DM	MALMAS, MMAS-8
Cohen et al. (2010) [15]	USA	Clinical trial	RCT	526	55.5(7.3)	67.0%	OGM	PR, MGLS, SDSCA

Description of included studies (N=71)

Gonzalez et al. (2013) [16]	USA	Health care	Cross-sectional	170	55.6 (9.6)	66.5%	OAM	% time medication taken last month, ACTG, SDSCA, MEMS
Kheir et al. (2010) [17]	Qatar	Health care	Cross-sectional	54	50.0 (9.6)	61.0%	Metformin	MEMS, PC
Lee et al. (2013) [18]	Korea	Health care	Prospective	317	59.3 (11.2)	38.5%	NR	MMAS-8
Liau et al. (2019) [19]	Singapore	Health care	Prospective	393	59.4 (12.2)	50.9%	DM	2-items doses taken past 7 days
López-Simarro et al. (2016) [20]	Spain	Health care	Cross-sectional	320	67.5 (10.7)	46.6%	DM, AM, LLM	H-S test, PR
Mikhael et al. (2019) [21]	Iraq	Health care	Cross-sectional	84	55.3 (9.0)	38.1%	DM	IADMAS
Osborn & Gonzalez (2016) [22]	USA	Health care	Cross-sectional	144	50.7 (11.9)	61.1%	IT	MIAS, ARMS, SDSCA, 2-items doses taken past 7 days
Sakthong et al. (2009) [23]	Thailand	Health care	Cross-sectional	303	61.1 (11.4)	23.4%	HM, IT	MMAS-8
Sutton et al. (2014) [24]	UK	Clinical trial	RCT	226	63.2 (10.9)	35.0%	OGM	MARS-5
Tandon et al. (2015) [25]	USA	Health care	Cross-sectional	154	57.5 (10.0)	73.0%	DM	MMAS-8
Torre et al. (2018) [26]	Portugal	Health care	Prospective	1328	64.1 (11.4)	49.3%	DM, IT	PR, packages refilled
Vluggen et al. (2019) [27]	Netherlands	Health care	Prospective	312	60.8 (6.8)	33.0%	OHA	ProMAS, MARS-5
Wang et al. (2012) [28]	Singapore	Health care	Cross-sectional	294	58.0 (9.0)	47.6%	OAM	MGLS
Zongo et al. (2016a) [29]	Canada	Health care	Cross-sectional	153	MDN=64.3 (NR)	37.9%	GH	SR-4, MMAS-8, % pills missed last 7 days, 1-item ADT
Zongo et al. (2016b) [30]	Canada	Health care	Cross-sectional	901	MDN=64.2 (NR)	41.4%	DM	MMAS-8
Epilepsy (*n*=1)								
Margolis et al. (2018) [31]	USA	Health care	Cross-sectional	50	42.0 (14.0)	60.0%	Antiepileptic	MEMS, rate medication taken
HIV/AIDS (*n*=5)								
Bangsberg et al. (2001) [32]	USA	Health care	Cross-sectional	42	NR	NR	ART	EMD, AEMD, PDDT, PC
Deschamps et al. (2004) [33]	Belgium	Health care	Prospective	43	MA=43.2 (8.8) MNA=41.0 (8.0)	MA=19.0%, MNA=12.0%	ART	MEMS, SR scale, Physician report

Description of included studies (N=71)

Gao & Nau (2000) [34]	USA	Health care	Cross-sectional	65	25-44=77.4%	24.6%	ART	MGLS, % doses taken past 2 days & 2 weeks
Kabore et al. (2015) [35]	USA	Health care	Cross-sectional	269	2.3 (9.3)	12.6%	ART	Ability to take medication, ACTG, VAS, PR
Llabre et al. (2006) [36]	USA	Health care	Cross-sectional	323	41.0 (8.5)	41.5%	ART	MEMS, ACTG, MATI
Hypertension (*n*=33)								
Adedokun & Oladipo (2012) [37]	Nigeria	Health care	Cross-sectional	77	40-64=85.3%	36.0%	AM	MMAS-5, e-CAP
Cabral et al. (2018) [38]	Portugal	Health care	Cross-sectional	423	68.2 (10.5)	53.2%	AM	MUAH
Chatziefstratiou et al. (2015) [39]	Greece	Health care	Retrospective	68	65.5 (12.6)	44.1%	AM	HK-LS
Christensen et al. (2009) [40]	Denmark	Clinical trial	RCT	398	NR	52.5%	AM	Days medications taken past week, HHDC
Durand et al. (2018) [41]	Ireland	Clinical trial	Cross-sectional	204	69.9 (10.7)	42.2%	AM	MMAS-8, MARS-5, PR, Urine analysis
Fernandez et al. (2008) [42]	USA	Health care	RCT	168	54.0 (12.4)	86.0%	AM	MASES-R
Gallagher et al. (2015) [43]	USA	Health care	Cross-sectional	149	64.0 (9.0)	72.0%	AM	MedSignals pillbox, MMAS-8, VAS
Gregoire et al. (1997) [44]	Canada	Health care	Cross-sectional	109	63.9 (9.1)	66.1%	AM	PR, PC
Hamilton (2003) [45]	Norway	Clinical trial	RCT	107	58.0 (NR)	48.6%	AM	MEMS, MOS-GAS, VAS, MGLS, Shea-3, Haynes-1, Collateral report, Capsule count, Urinary potassium excretion
Hansen et al. (2009) [46]	USA	Clinical trial	RCT	806	59.0 (10.0)	71.0%	AM	MEMS, MGLS, PR
Jankowska-Polanska et al. (2016) [47]	Poland	Health care	Cross-sectional	110	60.7 (12.6)	54.6%	AM	MMAS-8
Kim et al. (2014) [48]	Korea	Health care	Cross-sectional	373	57.2 (11.2)	45.0%	AM	MMAS-8
Koschack et al. (2010) [49]	Germany	Health care	Cross-sectional	353	64.0 (11.0)	49.0%	AM	HBCS, MGLS

Description of included studies (N=71)

Krousel-Wood et al. (2009) [50]	USA	Health care	Cross-sectional	87	76.0 (NR)	NR	AM	MMAS-8, PR
Krousel-Wood et al. (2013) [51]	USA	Health care	Cross-sectional	394	76.6 (5.6)	66.0%	AM	PR, MMAS-8, HBCS
Lambert et al. (2006) [52]	Africa	Health care	Cross-sectional	98	52.0 (7.6)	51.0%	AM	HBCS
Lim et al. (1992) [53]	Malaysia	Health care	Cross-sectional	168	52.0 (NR)	42.0%	AM	PC, Interview questions
Lomper et al. (2018) [54]	Poland	Health care	Cross-sectional	279	66.5 (11.0)	59.5%	AM	ARMS
Márquez-Contreras et al. (2018) [55]	Spain	Health care	Prospective	102	61.1 (9.1)	68.6%	AM	MEMS, e-prescription program
Nobles et al. (2018) [56]	USA	Health care	Cross-sectional	437	OAS=62.5 (8.9) TRS=65.8 (11.6) LTS=66.6 (13.6) MMS=67.0 (12.1)	63.5%	AM	Developed questionnaire
Okello et al. (2016) [57]	Uganda	Health care	Cross-sectional	329	MDN=55.0 (NR)	69.0%	AM	MMAS-8
Pandey et al. (2015) [58]	USA	Health care	Retrospective	47	52.5 (2.0)	46.8%	AM	MMAS-8, Drug monitoring
Petry et al. (2015) [59]	USA	Clinical trial	RCT	29	50.4 (11.0)	55.2%	AM	PC, MMAS-8
Prado et al. (2007) [60]	Brazil	Health care	Cross-sectional	109	Over 60=53.7%	71.6%	AM	PC, MGLS, HBP control, HBP knowledge, developed question
Schroeder et al. (2006) [61]	UK	Clinical trial	RCT	245	IG=67.9 (10.3) CG=68.2 (9.4)	45.0%	BPLM	Developed questionnaire, MEMS
Shin & Kim (2013) [62]	Korea	Health care	Cross-sectional	92	73.2 (6.5)	79.3%	AM	MMAS-8
Tedla & Bautista (2017) [63]	USA	Health care	Prospective	175	50.0 (NR)	43.0%	AM	MARS-5, PC, SRA-1M
Uchmanowicz et al. (2016) [64]	Poland	Health care	Cross-sectional	117	60.8 (12.4)	54.7%	AM	HBCS
van de Steeg et al. (2009) [65]	Germany	Health care	Cross-sectional	128	71.1 (NR)	52.0%	AM	MGLS, MARS-5, GP's electronic database
Voils et al. (2012) [66]	UK	Health care	Cross-sectional	202	64.1 (11.0)	14.0%	AM	5-items doses missed past 7 days, MMAS-8

Description of included studies (N=71)

Wang et al. (2004) [67]	USA	Health care	Cross-sectional	200	66-75=36.0%	40.5%	AM	2-questions, PR
Wetzels et al. (2006) [68]	Netherlands	Health care	Cross-sectional	283	NR	50.0%	AM	BMQ, PR, MEMS, MUAH
Zeller et al. (2008) [69]	UK	Health care	Cross-sectional	239	66.7 (10.3)	47.7%	BPLM	ASRQ, MEMS
Various conditions (*n*=2)								
Chan et al. (2020) [70]	UK	Health care	Cross-sectional	428	Asthma=49.1 (18.1) Diabetes=58.2 (15.9) Hyper.A= 62.3 (13.4) Hyper.B= 53.6 (14.6)	41.8%	NR	MARS-5
Surekha et al. (2016) [71]	India	Health care	Cross-sectional	180	Overall=59.1 (11.0)	57.8%	AM, DM	MMAS-8

Note. CG= Control Group; IG= Intervention Group; LTS= Likert-Type Scale; MA= Medication Adherence; MNA= Medication Non-Adherence; MDN= Median; MMS= Multiple Medication Scales; OAS= Original Adherence Scale; TRS= Time Reference Scale.

[1]Studies are listed alphabetically based on condition and then alphabetically by author.

[2]Clinical trials: experiments or observations designed to answer specific questions about interventions (e.g., as novel drugs); Health care/routine care: regular care that patients got from their doctors/physicians.

[3]For the studies that the mean age was not reported, frequencies/median were reported instead.

[4]AMM= Asthma maintenance medications; AM= Antihypertensive medication; ART= Antiretroviral therapy; BPLM= Blood pressure lowering medication; CM= Cancer medication; DM= Diabetes medication; DMI= Daily multiple injections; ET= Endocrine therapy GH= Glycated hemoglobin; HM= Hypoglycemic medications; ICS= Inhaled corticosteroids; IT= Insulin treatment; LLM= Lipid-lowering medication; OAM= Oral antidiabetic medication; OGM= Oral glucose medication; OHA= Oral hypoglycaemic agents; PD= Palliative drugs.

[5]AAAQ= Adult Asthma Adherence Questionnaire; ACTG= AIDS Clinical Trials Group; ADRD=Administrative drug-reimbursement database; ADT= Antidiabetes drug treatment; AEMD= Adjusted electronically monitored doses; ARMS= Adherence to Refills and Medications Scale; ASRQ= Adherence self-report questionnaire; BMQ= Beliefs about Medicines Questionnaire; DMAS= Diabetes Medication Adherence Scale; EMD= Electronic monitored doses; HBCS= Hill-Bone High Blood Pressure Compliance Scale; HBP=High Blood Pressure; HHDC= Helping Hand Data Capture; HK-LS= Hypertension Knowledge-Level Scale; H-S test= Haynes-Sackett adherence test; IADMAS= Iraqi Anti-Diabetic Medication Adherence Scale; MALMAS= Malaysian Medication Adherence Scale; MARS-5= Medication Adherence Report Scale; MARS-A= Medication Adherence Report Scale for Asthma; MASES-R= Medication adherence self-efficacy scale; MAT-CP= Medication assessment tool for cancer pain management; MATI= Medication Adherence Training Instrument; MEMS= Medication Event Monitoring System; MGLS= Morisky Green Levine Medication Adherence Scale; MIAS= Morisky Medication Adherence Scale to insulin adherence; MMAS-8= Morisky Medication Adherence Scale-8 items; MOS-GAS= Medical outcomes study-General Adherence Scale; MUAH= Maastricht Utrecht Adherence in Hypertension; PC= Pill count; PDDT= Percentage of days dose taken; PR= Pharmacy Refill; ProMAS= Probabilistic Medication Adherence Scale; SCI-R= Diabetes Self-Care Inventory-Revised Version; SDSCA= Summary of Diabetes self-care activities measure; SMAQ= Simplified Medication Adherence Questionnaire; SR=Self-report; SR-4= 4-item self-report medication adherence scale; SRA-1M= Self-reported adherence during last month; VAS= Visual analogue scale.

Table 2

Summary of findings regarding quality indicators of included measures from all studies

Measure[1]	N of countries in which was used	Average Sample Size (Range)	Internally consistent[2,3,4] (Cronbach's alpha)	Correctly identifying MA[2,3,5] (Sensitivity, %)	Correctly identifying MNA[2,3,5] (Specificity, %)	Probability to correctly identify MA[2,3,5] (PPV, %)	Probability to correctly identify MNA[2,3,5] (NPV, %)	Stable over time[2,3,6] (Pearson's/ Spearman's)	Feasible [2,3,7] (%)	Correlation/ agreement with NSR/ SR[2,3,8,9] (Pearson's/ Spearman's/ Cohen's k)
	Mean (Range)									
Self-Reports: 27 measures										
Non-condition-specific										
ARMS (k=2)	2	212 (144-279)	.95 (.27-.67)	78	80	-	-	-	-	-
Developed questions on doses taken/missed (k=15)	7	258 (43-806)	.52	49 (17-88)	69 (19-95)	60 (33-86)	49 (20-79)	.51 (.45-.56)	-	.37 (-.29-.76)
MALMAS (k=1)	1	84	.69	-	-	-	-	.71	-	-
MARS-5 (k=8)	6	319 (128-840)	.77 (.70-.82)	15 (9-20)	94 (90-97)	67	64	.97	-	.31 (-.27-.74)
MGLS (k=10)	7	314 (65-840)	.58 (.25-.73)	50 (32-74)	62 (45-73)	44 (28-86)	67 (41-80)	.60	-	.28 (.21-.37)
MMAS-8 (k=18)	9	228 (29-901)	.64 (.47-.81)	57 (26-80)	68 (48-89)	60 (30-84)	65 (43-92)	.26 (.47-.91)	-	.62 (.17-.84)
MOS-GAS (k=1)	1	107	.88	-	-	-	-	-	-	.27
ProMAS (k=1)	1	312	-	-	-	-	-	-	-	-
SMAQ (k=1)	1	242	.67	-	-	-	-	-	-	.19
VAS (k=2)	1	209 (149-269)	-	26 (18-34)	92 (85-98)	71	55	-	-	-
Condition-specific										
AAA-Q (k=1)	1	420	.50	73	45	64	55	-	-	-
ACTG (k=3)	1	254 (170-323)	.42	27	85	67	48	-	-	.27
ASRQ (k=1)	1	239	-	46	66	24	84	-	-	.73
DMAS (k=1)	1	500	.61	70	52	74	47	-	-	-
HBP control (k=1)	1	109	-	56	72	46	78	-	-	-
HBCS (k=4)	3	241 (98-394)	.77 (.73-.80)	41 (27-54)	69 (63-75)	23	78	-	-	-
HK-LS (k=1)	1	68	.66	-	-	-	-	-	-	-
H-S test (k=1)	1	320	-	-	-	-	-	-	-	NS

Summary of findings regarding quality indicators of included measures from all studies

IADMAS (k=1)	1	84	.71	100	34	31	100	.81	-	-
Interview questions (k=1)	1	168	-	71	50	80	38	-	-	.75
Knowledge of HBP (k=1)	1	109	-	56	72	46	78	-	-	-
MARS-A (k=2)	2	174 (53-294)	.85	82	69	-	-	-	-	.42
MASE-R (k=1)	1	168	.91	-	-	-	-	.51	-	.20
MAT-CP (k=2)	2	105 (101-109)	-	-	-	-	-	.89 (.86-.92)	-	-
MATI (k=1)	1	323	.49	-	-	-	-	-	-	.32
MUAH (k=2)	2	353 (283-423)	.69 (.64-.74)	-	-	-	-	-	-	-.34
SDSCA (k=2)	1	348 (144-526)	-	-	-	-	-	-	-	.33 (.21-.39)
Non-Self-Reports: 10 measures										
AEMD (k=1)	1	42	-	87	83	88	83	-		-
Biochemical Analysis (k=3)	3	184 (107-242)	-	-	-	-	-	-	-	.33
e-CAP (k=1)	1	77	-	-	-	-	-	-	-	.06
E-prescription program (k=1)	1	279	-	60	92	67	90	-	-	-
MDI-log monitor (k=1)	1	53	-	-	-	-	-	-	-	.42
MedSignals pillbox (k=1)	1	149	-	18	98	-	-	-	91	-
MEMS (k=9)	5	231 (43-806)	-	77	83	93	56	-	-	.20
Pharmacy Refills/Record (k=9)	9	345 (87-806)	-	69 (46-92)	77 (65-89)	96	79	-	-	.36 (.10-.37)
Physician Claims/Report (k=1)	1	692	-	-	-	-	-	-	-	.04
Pill Count (k=7)	5	98 (29-175)	-	39	59	-	-	-	-	.80 (.63-.91)

Note. - =Not Reported; NS= Non-Significant.

[1]AAA-Q= Adult Asthma Adherence Questionnaire; ACTG= AIDS Clinical Trials Group; AEMD= Adjusted Electronic Monitored Doses; ARMS= Adherence to Refills and Medications Scale; ASRQ= Adherence Self-Report Questionnaire; DMAS= Diabetes Medication Adherence Scale; HBP=High Blood Pressure; HBCS= Hill-Bone Compliance to High Blood Pressure Therapy Scale; HK-LS= Hypertension Knowledge-Level Scale; IADMAS= Iraqi Anti-Diabetic Medication Adherence Scale; MA= Medication Adherence; MALMAS= Malaysian Medication Adherence Scale; MNA= Medication Non-adherence; MARS-5= Medication Adherence Report Scale; MARS-A= Medication Adherence Report Scale-Asthma; MASE-R= Medication Adherence Self-Efficacy Scale; MAT-CP= Medication Assessment Tool for Cancer Pain; MATI= Medication Adherence Training Instrument; MDI= Metered-Dose Inhaler; MEMS= Medication Event Monitoring System; MGLS= Morisky Green Levine Medication Adherence Scale; MMAS-8= Morisky Medication Adherence Scale-8 item; MOS-GAS= Medical outcomes study-General Adherence Scale; MUAH= Maastricht Utrecht Adherence in Hypertension; NSR= Non-self-reportProMAS= Probabilistic Medication Adherence Scale; SCI-R= Self-Care Inventory-Revised Version; SDSCA= Summary of Diabetes self-care activities measure; SMAQ= Simplified Medication Adherence Questionnaire; SR= Self-report; VAS= Visual Analogue Scale.

[2]When more than one study reported values for an indicator, the average value was reported.
[3]Based on the interpretation of each indicator, the colors show that the reported values are: ●Low ●Moderate ●High
[4]Low: coefficient <.70, High: coefficient ≥.70;
[5]Low: percentage <80, High: percentage≥80;
[6] Low: coefficients<.80, Moderate: coefficients=.80-.90, High: coefficients≥.90;
[7]High: higher percentages indicate higher acceptability of the measure;
[8]For self-reports high agreement with non-self-reports reported, whereas for non-self-reports the agreement with self-reports reported.
[9]Low: coefficients<.40, Moderate: coefficients=.40-.80, High: coefficients≥.80.

Abbreviations used throughout the paper

Abbreviation	Definition
ACTG	AIDS Clinical Trials Group
AEMD	Adjusted Electronically Monitored Dose
ARMS	Adherence to Refills and Medications Scale
ASRQ	Adherence Self-report Questionnaire
BQT	Barriers Questionnaire-Taiwan form
DMAS	Diabetes Medication Adherence Scale
EMD	Electronic Monitored Dose
HCBS	Hill-Bone Compliance to High Blood Pressure Therapy Scale
HHDC	Helping Hand Data Capture
H-S test	Haynes–Sackett (H–S) test
IADMAS	Iraqi Anti-Diabetic Medication Adherence Scale
MA	Medication Adherence
MALMAS	Malaysian Medication Adherence Scale
MARS	Medication Adherence Report Scale
MARS-A	Medication Adherence Report Scale for Asthma
MASE-R	Medication Adherence Self-Efficacy Scale
MDI	Metered-Dose Inhaler
MEMS	Medication Event Monitoring System
MGLS	Morisky Green Levine Medication Adherence Scale
MMAS	Morisky Medication Adherence Scale
MNA	Medication Non-Adherence
MOS-GAS	Medical outcomes study-General Adherence Scale
MUAH	Maastricht Utrecht Adherence in Hypertension
NPV	Negative Predictive Value
PDDT	Percentage of Days Doses Taken
PPV	Positive Predictive Value
ProMAS	Probabilistic Medication Adherence Scale
SMAQ	Simplified Medication Adherence Questionnaire
VAS	Visual Analog Scale
WHO	World Health Organization

Appendix A

Search Terms

"medication", "medication adherence", "medication intake", "medication concordance", "medication compliance", and "medication non-adherence" combined with the terms "assessment", "measurement", "monitoring", "electronic", "self-report", or "objective", and "asthma", "diabetes", "hypertension", "blood pressure", "epilepsy", "cancer", "HIV" or "HIV/AIDS"

Search Strategy

a) Search strategy PsycInfo

(1) ((TI medication adherence) OR (TI medication non-adherence) OR (TI medication intake) OR (TI medication concordance) OR (TI medication compliance) OR (TI medication)) AND ((TI assessment) OR (TI measurement) OR (TI monitoring) OR (TI electronic) OR (TI self-report) OR (TI objective)) AND ((TI asthma) OR (TI diabetes) OR (TI hypertension) OR (TI blood pressure) OR (TI epilepsy) OR (TI cancer) OR (TI HIV) OR (TI AIDS))

(2) ((AB medication adherence) OR (AB medication non-adherence) OR (AB medication intake) OR (AB medication concordance) OR (AB medication compliance) OR (AB medication)) AND ((AB assessment) OR (AB measurement) OR (AB monitoring) OR (AB electronic) OR (AB self-report) OR (AB objective)) AND ((AB asthma) OR (AB diabetes) OR (AB hypertension) OR (AB blood pressure) OR (AB epilepsy) OR (AB cancer) OR (AB HIV) OR (AB AIDS))

b) Search strategy Pubmed

(1) ((medication adherence[Title/Abstract]) OR (medication non-adherence[Title/Abstract]) OR (medication intake[Title/Abstract]) OR (medication compliance[Title/Abstract]) OR (medication concordance[Title/Abstract]) OR (medication[Title/Abstract])) AND ((assessment[Title/Abstract]) OR (measurement[Title/Abstract]) OR (monitoring[Title/Abstract]) OR (electronic[Title/Abstract]) OR (self-report[Title/Abstract]) OR (objective[Title/Abstract])) AND ((asthma[Title/Abstract]) OR (diabetes[Title/Abstract]) OR (hypertension[Title/Abstract]) OR (blood pressure[Title/Abstract]) OR (epilepsy[Title/Abstract]) OR (cancer[Title/Abstract]) OR (HIV[Title/Abstract]) OR (AIDS[Title/Abstract]))

c) Search strategy Scopus

(1) (TITLE-ABS-KEY (medication AND adherence) OR TITLE-ABS-KEY (medication AND nonadherence) OR TITLE-ABS-KEY (medication AND intake) OR TITLE-ABS-KEY (medication AND concordance) OR TITLE-ABS-KEY (medication AND compliance) OR TITLE-ABS-KEY (medication) AND TITLE-ABS-KEY (assessment) OR TITLE-ABS-KEY (measurement) OR TITLE-ABS-KEY (monitoring) OR TITLE-ABS-KEY (electronic) OR TITLE-ABS-KEY (self-report) OR TITLE-ABS-KEY (objective) AND TITLE-ABS-KEY (asthma) OR TITLE-ABS-KEY (diabetes) OR TITLE-ABS-KEY (hypertension) OR TITLE-ABS-KEY (blood AND pressure) OR TITLE-ABS-KEY (epilepsy) OR TITLE-ABS-KEY (cancer) OR TITLE-ABS-KEY (HIV) OR TITLE-ABS-KEY (AIDS))

Note. TI= Title; AB= Abstract; ABS= Abstract

Appendix B

References of included studies

1. Cohen JL, Mann DM, Wisnivesky JP, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Ann Allergy, Asthma Immunol*. 2009;103(4):325-331. doi:10.1016/S1081-1206(10)60532-7

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Appendix C

Data extracted from each study

1) Characteristics of the study: year of publication, location, research design, purpose of measuring adherence (i.e., clinical trial: experiments or observations designed to answer specific questions about an intervention vs. health care/routine care: regular care that patients got from their doctors/physicians);

2) Characteristics of the population: type of chronic condition, sample size, age, gender;

3) Characteristics of adherence: type of medication, definition of MA, percentage of MA;

4) Assessment of MA: method used to assess MA;

5) Quality indicators of assessment method(s): internal consistency, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), feasibility, convergent validity (where relevant), and other psychometric properties.

Appendix D

Formulas used to compute Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

$$PPV = \left[true\frac{positive}{true\ positive + false\ positive}\right] * 100$$

$$NPV = \left[true\frac{negative}{true\ negative + false\ negative}\right] * 100$$

Example Bangsberg et al. (2001) [32]:

Adjusted Electronically Monitored Doses (AEMD):

$PPV = \left[\frac{21}{21+3}\right] * 100 \quad NPV = \left[\frac{15}{15+3}\right] * 100$