Patient-reported outcome measures to detect intentional, mixed, or unintentional non-adherence to medication: a systematic review

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ABSTRACT
Objective To categorise patient-reported outcome measures (PROMs) into their propensity to detect intentional and/or unintentional non-adherence to medication, and synthesise their psychometric properties.

Design Systematic review and regression analysis.

Eligibility Medication adherence levels studied at primary, secondary and tertiary care settings. Self-reported measures with scoring methods were included. Studies without proxy measures were excluded.

Data sources Using detailed searches with key concepts including questionnaires, reliability and validity, and restricted to English, MEDLINE, EMBASE, CINAHL, International Pharmaceutical Abstracts, and Cochrane Library were searched until 01 March 2022. Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA-2020) checklist was used.

Data analysis Risk of bias was assessed via CONSORT-based Standards for the selection of health Measurement Instruments (COSMIN-2018) guidelines. Narrative synthesis aid by graphical figures and statistical analyses.

Outcome measures Process domains (behaviour (e.g., self-efficacy), barrier (e.g., impaired dexterity) or belief (e.g., perception)), and overall outcome domains of either intentional (I), unintentional (UI), or mixed non-adherence.

Results Paper summarises evidence from 59 studies of PROMs, validated among patients aged 18–88 years in America, the United Kingdom, Europe, Middle East, and Australasia. PROMs detected outcome domains: intentional non-adherence, n=44 (I=491 criterion items), mixed intentionality, n=13 (I=79/UI=50), and unintentional, n=2 (UI=5). Process domains detected include belief (383 criterion items), barrier (192) and behaviour (165). Criterion validity assessment used proxy measures (biomarkers, e-monitors), and scoring was ordinal, dichotomised, or used Visual Analogue Scale. Heterogeneity was revealed across psychometric properties (consistency, construct, reliability, discrimination ability). Intentionality correlated positively with negative beliefs (r(57)=0.88) and barriers (r(57)=0.59). For every belief or barrier criterion-item, PROMs’ aptitude to detect intentional non-adherence increased by β=0.79 and β=0.34 units, respectively (R²=0.94). Primary care versus specialised care predicted intentional non-adherence (OR 1.9; CI 1.01 to 2.66).

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ While the processes leading to the final classification can be subjected to individual interpretation of the items’ construct and consequences to treatment default, the twofold approach to first, classify every PROM item, and second, to classify the overall PROMs into outcome domains depending on the dominance of item type, demonstrated good inter-rater reliability.
⇒ Using regression analysis of process and outcome domains, some insights were gained on the reasons for non-adherence. However, for future studies, further analysis with greater sample sizes are recommended.
⇒ The process domains of behaviour (habitual), barrier (tangible impediment), or belief (mindset) were not only difficult to assess by means of self-reported outcome measures, but were also revealed as the real challenges to fostering adherence.
⇒ While we had juxtaposed scores against proxy measures, as with any self-reported data, limitations existed with the accuracy of recall and fair reporting of events.

Conclusions Ten PROMs had adequate psychometric properties. Of the ten, eight PROMs were able to detect total, and two PROMs were able to detect partial intentionality to medication default. Fortification of patients’ knowledge and illness perception, as opposed to daily reminders alone, is most imperative at primary care levels.

INTRODUCTION
The act of taking medication is deemed fitting when it is done in accordance to instructions given by healthcare professionals. In general, the patient is instructed to take an accurate dose, at a predetermined time interval. Poor medication adherence poses a serious and expensive challenge to patients and healthcare systems. The Centers for Disease Control estimated that each year, the death of 125,000...
persons in the USA alone was caused by treatment failure for chronic diseases and default in taking prescribed medications regularly and accurately. In addition, $300 billion USD (approx. £228 billion) was spent on hospitalisation, emergency admissions and clinic visits.\(^1\)

Intentional and unintentional non-adherence are usually distinguished by patients' medication-taking conduct, which is influenced by, firstly, processes such as pre-emptive thoughts or behavioural aspects, which eventually lead the patients to take their medication (e.g., to get better, habitual, or due to medication stock availability). Secondly, medication-taking conduct is distinguished by the outcome or action, i.e., patient ended up forgetting, skipping a dose, changing the amount, or delaying the time at which a medication should be taken, or did not take medication on purpose.\(^2\) As the nature of instructions for medication-taking is often complex and varied depending on an individual's pre-existing medical conditions and concomitant medications, the criteria for adherence assessment are also subjective. Ideally, an adherence measure is developed to detect common predictors that may influence adherence for a diseased population.

Existing measures have commonly explored forgetfulness as an obstacle to adherence and subsequently identified instances where forgetting may be more frequent, such as, when away from home, during weekends, or when travelling for work.\(^3\) Intuitively, many measures also explored psychosocial aspects, such as, attitudes and perceptions associated with belief (e.g., their medication is not working, they do not need to take ‘too much of’ the medication). Nevertheless, users have critiqued that although such patient-administered questionnaires addressed specific obstacles to medication adherence, they were disease-specific, and hence had limited use in the general clinical care setting.\(^4\) In addition, the vulnerable older adults, who most require the assessment, were often excluded from the surveys as they presented with visual or cognitive impairment, and could not communicate effectively.

Several self-reported adherence measures, such as the Morisky scale,\(^5\) were established to screen for the possibility of missed doses or timings, and have been widely incorporated in clinical practice because of their ease of use. However, measures that assess only the instances of non-adherence offer little insights into the myriad of possibilities contributing to such misconduct, such as, the lack of motivation or specific difficulties encountered that could impact one’s adherence.\(^6\) To the best of our knowledge, this is the first systematic review that characterises patient-reported outcome measures (PROMs) of medication non-adherence, and distinguishes between intentional and unintentional causes. For the purpose of this review, intentional non-adherence is defined as instances when a patient is in a conscious and aware state of mind, and subsequently decides against following the recommendations of healthcare professionals.\(^7\) The patient is mindful of his or her decision, and had consciously weighed the pros and cons of adhering to treatment. Unintentional or sporadic non-adherence, in contrast to intentional causes, is consequential to a passive process i.e., unlikely associated with one’s implicit judgement.\(^8\) Patients can unintentionally non-adhere to their medication, i.e., when forgetful, careless, or have limited physical dexterity.

The aim of the systematic review was to critically appraise and synthesise PROMs in order to categorise their data into intentional and unintentional non-adherence to medication for chronic illnesses. The scope of this review is threefold: first, to establish studies where the level of non-adherence to medication was scored using validated and published self-reported measures (where adherence was reported, the scoring was reversed); second, to categorise each of the measure’s items/criteria (adherence related) to one of the three process domains: behaviour, barrier or belief, and to one of the three outcome domains: intentional, unintentional, or mixed; third, to categorise every measure into intentional, unintentional or mixed, based on the dominance or leading domain of its criterion item.

The term, ‘medication-taking conduct’ shall be used henceforth, and is defined as whether or not a patient is capable of taking medication in a manner judged to be congruent with the governing norms.

**METHODS**

**Design**

This review was developed and reported considering the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA-2020) checklist\(^9\) (checklist in online supplemental appendices 1 and 2) and in accordance with the CONsensus-based Standards for the selection of health Measurement INstruments 2018 (COSMIN-2018) guideline for systematic reviews of PROMs\(^10\) (see section on assessment of methodological quality). The protocol for this systematic review is available at https://doi.org/10.5061/dryad.8cz8w9gsq.

**Search strategy**

The search strategy was aimed at retrieving articles published in the English language, on validated patient-reported outcomes, which were direct reports from patients about their medication-adherence status. Grey literature was excluded from the search criteria. The following databases were searched from January 1980 until 1 March 2022: MEDLINE (EBSCO), EMBASE (EBSCO), CINAHL (EBSCO), International Pharmaceutical Abstracts (EBSCO) and the Cochrane Library. We combined three groups of keywords: those relating to patient-reported outcomes (e.g., self-report$, patient-report$), those relating to conformity towards instructions pertaining to medication taking (e.g., compliant$, adheren$, non-adheren$, poor adherence) and those relating to psychometric measures of adherence (e.g., validity, reliability, construct, instrument). The full
All titles and abstracts were independently screened by two reviewers, MLF and KMS. To identify relevant papers, the reference lists for articles that met the inclusion criteria were then reviewed. The reviewers were trained and a pilot with 30 papers was performed to guarantee an inter-reviewer agreement (until a kappa score of ≥0.75 was attained). Reasons for exclusions at the full-text screening process were recorded and discrepancies at any stage were resolved through discussions or a third reviewer consulted (KAMI) to reach a consensus.

A PRISMA flow chart summarises the process of selection (figure 1).

Data extraction and tabulation

Two reviewers (MLF and KMS) independently extracted the following data, where available, from the included articles:

- General characteristics of the study setting (year of publication, age, country).
- Characteristics of disease or condition: disease or condition studied, characteristics of the diseased respondents.
- PROMs’ characteristics: methods of administration, availability of electronic administration, response scale, domains, scoring, number and type of items, proxy measures of adherence (indirect and direct methods).
- Quality assessment of the psychometric properties of the PROMs (statuses on reliability and validity of measure/instrument).

Data from each study were tabulated using a standardised and pretested Word data collection form which was used for the purpose of achieving reliable inter-rater scores (online supplemental appendix 4). The corresponding author of the included articles was contacted via email for clarification or to request for additional information on any missing or unclear data. For the purpose of reporting, all terms related to adherence, such as compliance and concordance, were standardised and reported as adherence.

Data synthesis and analyses

Eligibility criteria

- Characteristics of participants: patients with chronic diseases and/or require drug therapy, including but not limited to recipients of renal transplants.
- Characteristics of the proxy measures: used another direct (e.g., biomarkers) or indirect (e.g., pill count, electronic monitors) method in addition to administering the PROM.
- Characteristics of the criterion items: statements, open or close-ended questions that can be binary coded, for example, medium and high adherence (adherent) versus low adherence (non-adherent).
- Characteristics of the process: analyses of primary data and coded into ‘behaviour’, ‘barrier’ or ‘belief’.

Eligibility

Initially, the items for each measure were generated and content validity assessed. The research must measure what it claims to have measured, i.e., the construct of each measure must be valid for the data to be valid. Subsequently, the scale was constructed, the questions pretested, survey administered, number of items reduced and the number of factors the scale captured was studied. During the evaluation phase of the scale, the number of dimensions, reliability and validity were assessed.

We report on the types of validity measured in the quantitative studies. For example, whilst one study described the process of developing the measure’s scale, other studies assessed the reliability and validity in various settings. In such cases where several studies used the same PROM, attempts were made to select the study in which the PROM was first featured or developed and validated.

Additionally, the following criteria were considered:

Inclusion criteria

1. Articles describing patient-reported and validated medication non-adherence measures development and/or validation.
2. Each item/criterion/subscale of a measure is guided by a statement or close-ended question. If the question is open-ended, the response is dichotomised.
3. At least two psychometric properties (reliability and/or validity) were assessed.
4. Included a proxy measure (employed a direct or indirect method to correlate adherence level with that evaluated by the measure).

Exclusion criteria

1. Articles where the scoring method or criteria for distinguishing the level or type of non-adherence could not be sourced.
2. Studies published only as abstracts or protocols.
3. PROMs’ items consisting of open-ended questions which were without a method of rating or scoring the adherence measure. This is because without the specification for scoring (for example, an answer of ‘yes’ carried one mark, towards the sum score), an overall assessment of adherence, i.e., poor, moderate or good, could not be performed.
4. Translation from an original English version into a different language.
Characteristics of the outcome: analyses of primary data and coded into ‘intentional (I)’, ‘unintentional (UI)’ or ‘mixed (I/UI)’ non-adherence.

Item classification (binning)

Items within outcomes and process domains were classified as follows:

1. Outcome domains: intentional, unintentional or not reported, and (2) process domains: behaviour, barrier or belief.

Guided by the Medication Adherence Model and the Health Belief Model, items which were phrased to incorporate an objective reasoning or a predetermined consequence of a medication-taking decision were classified as intentional. An example of an item is, ‘Did you take less than the amount prescribed when you started to feel an unpleasant side effect?’

We classified items as behaviour when the medication-taking conduct was attributed to one’s own responsibility. Where instructions on timings, doses and frequencies are adhered to, this behaviour is habitual and reflected self-efficacy, self-management skills, motivation, social support and discipline. An example of an item is, ‘I was careful not to miss a dose’. A tangible barrier comprised items addressing physical or practical aspects, for example, impaired manual dexterity, visual impairment, holidays, weekends, storage issues, prescription refills, cost and difficulty remembering, i.e., forgetting. Belief comprised items driving implicit judgements of the treatment or necessity beliefs—for example, perceptions, past negative experiences, knowledge on dosing, not taking when feeling better or taking only when feeling worse, trust and confidence in healthcare providers or the system. Online supplemental appendix 5 enlists the methods used to classify the PROMs’ items.

To ensure that the binning process was exhaustive, two independent reviewers (MLF and KMS) evaluated every PROM item for possible inclusion into any one of the three outcome and process domain categories depending on the nature of each criterion. The supplemental questions to the index question, for example, subquestions which explored reasons for ‘Did you forget to take your medication?’, such as ‘Did you forget to take when on holiday?—intentional (I)’ were identified as an additional item, which was then assigned to a domain.

In the final data synthesis, MLF and KMS independently assigned each PROM an overall category.
of either intentional (I), mixed of intentional and unintentional (I/UI) or unintentional (UI) depending on the coded items’ dominant or leading domain. Items of studies which aimed at measuring adherence (vs non-adherence) were reverse worded and scored. Any discrepancies were resolved via discussions or via a third reviewer (KAMI).

Assessment of methodological quality
MLF and KMS performed the quality assessment of the psychometric properties of the PROMs independently using the COSMIN guidelines. Each PROM’s development and its nine psychometric properties were assessed as ‘doubtful’, ‘inadequate’, ‘adequate’, ‘good’ or ‘very good’. In addition, we used Terwee et al’s psychometric quality criteria to assess and rate each criterion as ‘positive (+)’, ‘indeterminate (?)’ or ‘negative (−)’. In this review, we included PROMs which assessed and described a minimum of two psychometric properties.

Patient and public involvement
Patients or the public were not contacted nor involved in this study.

Statistical analyses
Kolmogorov-Smirnov test was used to test normality and subsequently the Spearman rank correlation was used to assess the correlation between outcome domain variables and process domains. Associations between measures’ increased intentionality (dependent variable) and their increasing behaviour or barrier or belief criterion items (independent variables) were studied in regression analyses. Type of patient care (dichotomous variable—primary care vs specialised care) was included in a logistic regression model, while the number of behaviour, barrier or belief criterion items (continuous variables) was included in linear regression models. Regression models were adjusted for age. Results from the logistic and linear regression analyses are presented as an OR and standardised beta coefficients (β) with 95% CIs, respectively. The level of statistical significance was set at p<0.05. The statistical analysis was performed with SPSS (version 24, SPSS Inc., Chicago, 147 IL, USA).

RESULTS
Search results and study characteristics
In total, 31,960 articles were retrieved from the five databases (figure 1). After removing duplicates, a further 28,600 articles were excluded based on the titles and abstracts (online supplemental appendix 6). Six hundred twenty relevant articles were identified from the reference lists. Hence, 3660 articles remained for full-text review. These articles were scrutinised against the paper’s inclusion and exclusion criteria. At this stage, 3601 articles were eliminated. In the span of four decades, i.e., from January 1980 through to March 2022, a total of 59 PROMs relevant to adherence were extracted—one from each of the remaining articles (n=59).

In instances where a number of studies utilised the same PROM, subsequent reporting for that PROM was based on the initial study in which the measure first appeared. As for methodological quality, the studies fulfilled the inclusion criteria of adequate description of at least two psychometric properties, for example, its content, construct, structural validity and/or reliability. Criterion validity was achieved by all included studies. This is because studies on PROMs that were juxtaposed against another standard or proxy measure were included, which meant that the studies included presented a correlate, i.e., a corresponding indirect or direct method employed in parallel with the PROMs to assess adherence. For instance, the pill count method, using an additional PROM, or data mining from medication possession ratio or from a medication events monitoring system, or direct measurements of biomarker plasma levels were undertaken.

The studies were conducted across regions of North and South America, Europe, Australasia, and in 16 countries, i.e., the USA (24), the United Kingdom (8), Canada (4), France (3), the Netherlands (3), Spain (3), Malaysia (2), Australia (2), China (1), Brazil (2), Hungary (1), Switzerland (2), Belgium (1), Germany (1), Romania (1) and Turkey (1). The respondents’ ages ranged from 18 to 88 years. The respondents included organ transplant recipients or patients receiving specified treatments for chronic conditions such as retroviral or cardiovascular diseases, kidney and endocrine disorders, ophthalmic conditions, gout, psychiatric illnesses or oncology. They were attending doctor appointments either at their general practice, or within secondary or tertiary care settings, or visiting primary healthcare facilities (community pharmacies, optometry services). Additionally, several patients were admitted from the emergency departments or hospitalised after surgery.

Evidence synthesis
Many of the PROMs were predominantly intentional followed by mixed intentionality and unintentional. These 59 PROMs yielded a total of 740 items/criteria that were related to adherence. Of those items, 572 were intentional in nature, 90 were unintentional and 78 did not report. Tables 1–3 depict the process and outcome domains assigned to individual criterion items, as well as the overall categorisation of each measure.

Outcome measures
Each measure or instrument was grouped into one of the three PROMs of non-adherence categories: table 1—intentional, I (n=44 of 59 instruments); or table 2—mixed, I/UI (n=13 of 59 instruments); or
Table 1  
PROMs of intentional (I) non-adherence—n=44 of 59 measures, 593 items

| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I/UL, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|---------------------------------------|---------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------|-----------------|--------------------------------------------------------|---------------------------------------------|
| 1  | Hogan et al, 1983, Canada 15 | Drug Attitude Inventory (DAI) | 1=30 Belief (30-stop taking when feeling better or worse, etc) | 30-item questionnaire E.g., feeling like a zombie after taking medication, take only when sick, unnatural to take medications, do not need medications once feel better, medication makes no difference and will do no harm if not taken | Habitual to occasional refusers of medications | Dichotomised scale high-low; yes=+2; no=+1 | Good discriminant validity and reliability ▶ Test-retest reliability=0.82 ▶ Internal consistency, Cronbach’s alpha=0.93 | Patients diagnosed with schizophrenia at a mental institution ▶ Mean age male: 40.0±12.8 ▶ Mean age female: 42.1±10.8 ▶ Juxtaposed against a 10-item (Van Putten & May) scale and clinical change over 3 weeks, as measured by the Brief Psychiatric Rating Scale |
| 2  | Morisky et al, 1986, USA 15 | Morisky, Green and Levine (MGL) Scale or MAQ | 1=3, not reported=1 Barrier (1-forgetting, Behaviour (1-careless), Belief (2-stopping medications when feeling better/worse) | 4-item questionnaire Forgetting, careless and stopping medications when feeling better or worse | High, medium, low adherence | Dichotomised scale high-low; yes=0; no=1 | Good concurrent & predictive validity ▶ Internal consistency, Cronbach’s alpha=0.61 | Patients with hypertension in 2 outpatient clinics of a large teaching hospital ▶ Median age (IQR): 54 (46-62) ▶ Juxtaposed against blood pressure measurements |
| 3  | Shea et al, 1992, USA 15 | Modified MSL Scale or MAQ | 1=2, not reported=3 Barrier (1-forgetting, Behaviour (2-careless, self-management ‘Do you ever miss your medication for any reason?’), Belief (2-stopping medications when feeling better/worse) | 5-item questionnaire derived from the 4 items developed by Morisky et al | More adherent (n=87) or less adherent (n=115) | Dichotomised scale high-low; yes=0; no=1 | Good concurrent & predictive validity ▶ Internal consistency, Cronbach’s alpha=0.71 | Patients with incidence of hypertensive urgency and emergency ▶ Mean age: 54.7±1.5 in less adherent group; mean age: 59.6±1.8 in more adherent group ▶ Juxtaposed against blood pressure measurements and emergency admissions |
| 4  | Barber et al, 1997, USA 15 | The Comparison of Ophthalmic Medications for Tolerability (COMTOL) Questionnaire | 1=3, not reported=1 4 questions on adherence: Barrier (1-forget), Behaviour (1-careless), Belief (2-stopping when feeling better, satisfaction) | 4 of 12 items assessed adherence Measured side effects and limitations in ADL /HRQoL, medication compliance and patient satisfaction with the medication | Higher scores (4 and 5)=higher adherence | 5-point Likert scale (where 5=I did not miss any dose, 4= rarily, 3=a few times, 2=fairly often and 1=usually, almost always and always) | Good-to-excellent internal consistency, Cronbach’s alpha=0.73–0.98 | Patients with open-angle glaucoma or ocular hypertension ▶ Mean age: 53.4± range 33–80 ▶ Juxtaposed against drugs’ known side effects and impact on ADL such as reading, driving or walking several blocks |
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|------------------------|--------------------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------------------------|-------------------|---------------------------------------------------|-------------------------------------------|
| 5  | Home and Weinman, 1999, UK17 | Beliefs about Medicine Questionnaire (BMQ) | I=18  
Belief (18): specific items (10); general items (8) | 18-item cognitive representation of medication  
2 subcales: BMQ: Specific scale, i.e., specific-necessity, specific-concerns; BMQ-General scale, i.e., general adherence and general harm | Higher scores in BMQ-General scale meant an overall negative perception of medication; High scores in the Specific-Concerns scale represented the notion that adverse reactions were potentially harmful when taking medication on a regular basis; High scores in the Specific-Necessity scale represented patient's need to adhere to medication to maintain health. | 5-point Likert scale with scores ranging from 4 to 20 | Good discriminant validity; the diabetic group had higher specific-necessity score; the asthmatic and psychiatric samples had higher specific-concerns score; patients attending the complementary clinic had higher scores for both general harm and overuse scales | Patients with asthma, diabetes and psychiatric conditions from hospital clinics and cardiac, general medical and renal (haemodialysis recipients) inpatients of hospitals  
A matched group of patients seeking care from allopathic (community pharmacy) and complimentary sources (homeopathy/ herbal clinic)  
Age range: 45.5–63.6  
Juxtaposed against IPQ, RAM and the Sensitive Soma Scale |
| 6  | Svarstad et al, 1999, USA6 | Brief Medication Questionnaire | I=7, UI=2  
Behaviour (7), Belief (2) | 9-item questionnaire to screen adherence and barriers to adherence  
5-item Regimen Screen that asks patients how they took each medication in the past week (How many times did you miss taking a pill?)  
2-item Belief Screen that asks about drug effects and bothersome features (How much it bothers you?)  
2-item Recall Screen about potential difficulties remembering (I stop or interrupt therapy, decrease the prescribed amount, take extra doses than prescribed) | Positive score ≥1 indicated positive screen for potential non-adherence or recall barriers; Belief barriers—Type of non-adherence in past week according to MEMS electronic prescribing: repeat=took at least 20% over or under the prescribed amount; sporadic=took 1%–19% over or under the prescribed amount | 4-point Likert scale (range=0–2) | Concurrent and predictive validity  
Discriminant validity: Regimen and Belief Screens had 80%–100% sensitivity for 'repeat' non-adherence  
Recall screen had 90% sensitivity for 'sporadic' non-adherence  
Non-adherence  
Mean age=52.6  
Juxtaposed against pill count |
| 7  | Thompson et al, 2000, Australia18 | Medication Adherence Rating Scale (MARS) | I=8, UI=2  
Barrier (1-forgotten), Behaviour (1-careless), Belief (8-stopping medications when feeling better/worse) | 10-item questionnaire  
E.g., thoughts are clearer, prevent getting sick, take when sick, and stop when feeling worse, feel unnatural/ weird/ tired/dizzy | Adherent or non-adherent | Dichotomised scale: yes=0; no=1 | Good concurrent and predictive validity, good discriminant and content validity  
Internal consistency, Cronbach's alpha=0.75 | Majority with schizophrenia, others with psychosis-like symptoms  
Mean: 32.9±11.1  
Juxtaposed against lithium levels and carer ratings of compliance |
### Table 1  Continued

| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|---------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------|---------------|---------------------------------|------------------|------------------------------------------------|-----------------------------------------------|
| 8  | Duong et al, 2001, France95 | Patient Medication Adherence Questionnaire | I=42, UI=13, not reported=6 | Barrier (13- ADL/routine affected, sociodemographics), Behaviour (12- self-confidence, support, motivation), Belief (36- adverse effect, comorbidities, knowledge, attitude, perception) | 61-item questionnaire  E.g., frequency of non-adherence, adverse effects, social support, psychological status, knowledge, attitudes, perception, alcohol and illicit drug use, socioeconomic status | Adherent or non-adherent | 4-point or 6-point Likert scale (ranging from strongly agree to strongly disagree) | Moderate predictive validity for half of the items (author suggested for future, PMAQ to focus on the variables identified as strong predictors of non-adherence) | Patients enrolled in Dijon Hospital AIDS day-care |
|    |                       |                                       |                                             | 8 Duong et al, 2001, France95 |                                           |               |                               |                                              | mean age: 40 (range: 21–79) | Juxtaposed against viral RNA level and plasma PI concentration |
| 9  | Horne and Weinman, 2002, UK20 | Medication Adherence Report Scale (MARS-9) | I=6, UI=1, not reported=2 | Barrier (1- forgetting), Behaviour (2- self-management), Belief (6- avoid if can, keep reserve medication, use when needed, alter dose, decide to miss, decide to take less) | 9-item questionnaire forgetting, taking, reasoning, feeling, taking, reason, medication, dose, decision, deciding | Higher scores=higher adherence | 5-point Likert scale (where 5=never, 4= rarely, 3=sometimes, 2=often and 1=very often) | Good construct and predictive validity  Cronbach's alpha 0.85 | Community-based asthma clinics |
|    |                       |                                       |                                             | 9 Horne and Weinman, 2002, UK20 |                                           |               |               |                                              | mean age: 49.3±8.1, age range: 16–84 years | Juxtaposed against IPQ and BMQ |
| 10 | Walsh et al, 2002, UK21 | Medication Adherence Self-Report Inventory (MASRI) | Not reported=12 | Behaviour (12-self-management, commitment, motivation) | 12 items with 2 themes  First part: 5 questions on missing doses and 1 question on VAS:  Second part: 4 questions on timing of doses and 2 on VAS | Adherent or non-adherent | Dichotomised scale: yes=0, no=1 | Moderate predictive validity (1 item), good discriminant and content validity (VARIOSCE) | HIV-infected adults from public specialist clinics |
|    |                       |                                       |                                             | 10 Walsh et al, 2002, UK21 |                                           |               |               |                                              | age range: 18–65 | Juxtaposed against MEMS, pill count and viral RNA level |
| 11 | De Klerk et al, 2003, Netherlands22 | Compliance Questionnaire Rheumatology (CQR -19) | I=15, UI=4 | Barrier (4-organiser used and stored strategically for ease of consumption, travelling/careless over weekends), Belief (15- trust in provider, stopping/after medications when feeling better/worse due to adverse effect/lack of efficacy) | 19-item questionnaire E.g., trust (and fear) in healthcare provider, fewer problems after taking medications, no alternatives, access to medication (practicalities and when on vacation) | Unsatisfactory or good adherence | 4-point Likert scale where 1=don’t agree at all; 2=don’t agree; 3=somewhat agree; 4=agree very much | Good discriminant and content validity, good reliability  Cronbach's alpha 0.71 | Outpatients at the rheumatology wards of 3 hospitals |
|    |                       |                                       |                                             | 11 De Klerk et al, 2003, Netherlands22 |                                           |               |                               |                                              | age range: 58–72 | Juxtaposed against pill count using MEMS |
Table 1 Continued

| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|--------------------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------|-------------------------------|-----------------|-----------------------------------------------|-----------------------------------------------|
| 12 | Godin et al, 2003, Canada\(^2\) | Self-Reported Questionnaire Assessing Adherence to Antiretroviral Medication | I=1, not reported=5 | Barrier (6- stop taking temporarily one or more antiretroviral medication during the last month)\(\uparrow\) 3. Pils missed the preceding day\(\uparrow\) 4. Pils missed the penultimate day\(\uparrow\) 5. Taking the initiative to take fewer pills of one or more antiretroviral medications during the last month\(\uparrow\) 6. Had missed taking one or more antiretroviral pills during the last month\(\uparrow\) | 6-item questionnaire Patients reported antiretroviral pills (n) missed on the preceding and penultimate days 3 questions used as aided-recall tools for situations that might have hampered the regular adherence to medication during the preceding 7 days 2 questions were used to assess non-adherence during the preceding 7 days Last question referred to the preceding 30 days as a time frame | Adherent or non-adherent (non-adherent if, for at least one measurement time, they reported having missed taking more than 5% of their pills on the preceding day) | 5-point Likert scale (ranging from strongly disagree to strongly agree) | Adequate predictive validity with only one item \(\uparrow\) Low sensitivity to detect increased viral load \(\uparrow\) Internal consistency, Cronbach’s alpha=0.76\(^2\) | HIV-infected patients from four clinics participated in a prospective longitudinal study \(\uparrow\) Mean age: 43±8.39 \(\uparrow\) Juxtaposed against change in viral load |
| 13 | Ogedegbe et al, 2003, USA\(^2\) | Medication Adherence Self-Efficacy Scale (MASES) | I=26 | Barrier (20- ADL/routine/lifestyle access to medication), Behaviour (4- self-management refill, motivation, self-efficacy), Belief (2- adverse effect, take when feeling better) | 26-item questionnaire measuring self-efficacy as a predictor of health behaviour E.g., how confident patients can take blood pressure medications on different occasions like when busy at home, when at work, when there is no one to remind, when worry about taking them for the rest of life, when they cause some side effects, when they cost a lot of money, when back home late from work, when do not have symptoms, when with family members, in public place, afraid of becoming dependent on them, afraid of affecting sexual performance, etc and how confident patients can carry out tasks such as filling prescription on time whatever the cost, etc | Adherent or non-adherent (where 1-not at all sure, 2= somewhat sure, 3=very sure and 4=does not apply) | 3-point Likert scale Good predictive and content validity Very good reliability \(\uparrow\) Internal consistency, Cronbach’s alpha=0.95\(^2\) | Ambulatory African-American patients with hypertension in 2 sequential phases in urban primary care \(\uparrow\) Mean age: 55.7±12.8; 58.9±12.6 \(\uparrow\) Juxtaposed against mean clinic blood pressure measurements |
### Table 1: Evaluation of Adherence to Immunomodulatory Therapy

| No | Author, year, country | PROM/scale/rating/ criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years), SD or IQR, correlates |
|----|----------------------|----------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------|------------------------------|-----------------|-----------------------------------------------|------------------------------------------|
| 14 | Atkinson et al, 2004, USA<sup>a</sup> | Treatment Satisfaction Questionnaire for Medication (TSQM) | I=14 | Barrier (3- ADL, convenience), Behaviour (4- confidence, motivation), Belief (7- adverse effect, knowledge) | 14 items | Adherent or non-adherent | 5-point or 7-point Likert scale or a VAS (ratio scale) | Good reliability and construct validity | Age range: 18-88 |
| 15 | Dolder et al, 2004, USA<sup>a</sup> | Brief Evaluation of Medication Influences and Beliefs (BEMIB) | I=7, UI=1 | Barrier (1- forgetting), Behaviour (4- confidence, motivation), Belief (3- adverse effect, knowledge) | 8 items | Adherent or non-adherent | 5-point Likert scale ranging from 1=completely disagree to 5=completely agree | Acceptable construct validity, acceptable reliability | Middle-aged and older outpatients at psychiatry clinics | Mean age: 57±12.1 |
| 16 | Chisholm et al, 2005, USA<sup>a</sup> | Immunosuppressant Therapy Barrier Scale (ITBS) | I=13 | Barrier (2- ADL, socioeconomic), Belief (11- adverse effect, frequency, and dose) | 13-item questionnaire | Adherent or non-adherent | 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree | Moderate construct and concurrent validity | Patients who underwent transplant and on immunosuppressant therapy | Mean age: 52±14.1; 54.79±14.3 |

<sup>a</sup> No Author, year, country; PROM/scale/rating/criteria/instrument; Outcome measure, number of intentional or unintentional items (I, UI, not reported); Process measure, item domain barriers (practical), behaviour (habit) or belief (perception); Item construct; Classification of non-adherence; Method of scoring; Psychometric properties, (reliability and/or validity); Setting, age* (years), SD or IQR, correlates.
| No | Author, year, country | PRO/OM scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain/barriers (practical), behaviour (habit) or belief (perception) | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years) | SD or IQR, correlates |
|----|----------------------|----------------------------------------|---------------------------------|-------------------------------------------------|-------------------------------|-----------------|---------------------------------|------------------|-----------------|
| 17 | Liu et al., 2006, USA | Adherence to antiretroviral therapy | I=9, not reported=3 | Barrier (3- forgetting), Behaviour (4- self-efficacy, support for taking antiretroviral), Belief (5-values placed on antiretroviral, healthcare providers, knowledge on resistance to antiretroviral) | 12 items on adherence | 3-point Likert scale ranging from 1-none of the time, 2-sometimes, 3-all the time | Good criterion and construct validity | 2 prospective longitudinal clinical investigations conducted at 5 HIV clinics | Mean age: 38.7±8.1 years | Juxtaposed against pill count, self-report, serum antiretroviral levels, MEMS and medication diaries |
| 18 | George et al., 2006, Australia | Beliefs and Behaviour Questionnaire (BBQ) | I=23, UI=2 | Barrier (8-forgetting, confusion, lifestyle changes/storage, routine, refill prescriptions), Behaviour (1-follow strictly), Belief (16-satisfaction with healthcare provider, stop taking depending on mood) | 25 items on adherence | 5-point Likert scale where 1=not at all and 5=extremely | Good validity and reliability | Ambulatory patients with chronic lung diseases | Mean age: 71.1±8.7 years | Juxtaposed against MARS |
| 19 | Wetzels et al., 2006, Netherlands | Maastricht Utrecht Adherence in Hypertension Questionnaire (MUH) | I=17, UI=2 | Barrier (3-forgetting, busy lifestyle), Behaviour (3-careless, lack of support, and discipline, unsure), Belief (13-stop taking when feeling better or worse, would take alternative, knowledge, aversion towards medication) | 19 items on medication adherence | 7-point Likert scale where 1=totally disagree to 7=totally agree | Good convergent validity | Patients on medication for hypertension and part of a randomised clinical trial from 2 regions in the Netherlands | Age range: 55–75 years | Juxtaposed against the BMQ, pharmacy refill records and MEMS |
| 20 | Glass et al., 2006, Switzerland | Swiss HIV Cohort Study Adherence Questions (SHCS-AQ) | Not reported=2 | Behaviour (2-self-management) | 2 items on adherence | Adherence defined in terms of missed doses (0, 1, 2 or >2) in the previous 28 days | Good concurrent and predictive validity | Outpatients from clinics of participating HIV centres, associated hospitals or specialised private practices | Mean age: 41.4±8.3 years | Juxtaposed against HIV viral load |
## Table 1

### Outcome measure, number of intentional or unintentional items (I, UI, not reported)

| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)SD or IQR, correlates |
|----|-----------------------|---------------------------------------|----------------------------------|------------------------------------------|-----------------|-----------------------------|-----------------|------------------------------------------|-----------------------------------------|
| 21 | Mannheimer et al, 2006, USA | Center for Adherence Support Evaluation (CASE) Adherence Index | I=1, not reported=2 | Barrier (1-difficult), Behaviour (2-self-management) | 5-item questionnaire E.g., a composite (sum) of 3 measures of antiretroviral therapy, difficulty taking on time, average number of days per week at least 1 dose missed, last time missed at least one dose | Adherence level categorised as 100%, 80%–99% and <80% | Timing: all, most, about half, very few, none in the past 7 days | Good predictive validity | Participants in a longitudinal, prospective cross-site evaluation of 12 adherence programmes throughout the USA | Mean age: 40.1±6.6 | Juxtaposed against HIV RNA level |
| 22 | Rissier et al, 2007, USA | The Self-Efficacy for Appropriate Medication Use Scale (SEAMS) | I=13 | Barrier (4-fill Rx, keep to appointment, inconvenience, routine), Behaviour (2-no social support, discipline), Belief (7-stop taking when feeling better or worse, alternative, knowledge, adverse effect towards medication) | 13 items from 21 on adherence, e.g., self-efficacy in adhering to prescribed medications | Adherent or non-adherent | 3-point Likert scale (where 1-not confident, 2=somewhat confident, and 3=very confident) | Good construct validity | Internal consistency, Cronbach’s alpha=0.89 | Patients with coronary heart disease (CHD) and other comorbid conditions | Mean age: 63.8±10.4 | Juxtaposed against Morisky scale |
| 23 | Gehi et al, 2007, USA | Single-item measure of self-reported adherence | I=1 | Behaviour (1-discipline) | Single item | Adherent or non-adherent, Non-adherence=taking medications as prescribed 75% of the time or less | 5-point Likert scale (where 1=all of the time and 5-less than half the time) | Good predictive validity | Outpatients with stable CHD | Mean age: 64±11 | Juxtaposed against cardiovascular events (CHD death, MI or stroke) |
| 24 | Prado et al, 2007, Brazil | Self-report on adherence frequency | I=1 | Behaviour (1-discipline) | Single item | Adherent or non-adherent, Dichotomised scale: yes=0; no=1 | Moderate predictive validity | Primary care hypertensives | 54% aged >60 | Juxtaposed against pill count |
| 25 | Byerly et al, 2008, USA | Brief Adherence Rating Scale (BARS) | Not reported=4 | Behaviour (4-self-management, commitment, motivation) | 4 items | Adherent or non-adherent, Nominal scale: number of days patient did not take or took less than half the time | Good concurrent and predictive validity; excellent reliability | Internal consistency, Cronbach’s alpha=0.92 | Outpatients with schizophrenia and schizoaffective disorder from public mental health clinics | Mean age: 40±8.1; age range: 21–59 | Juxtaposed against MEMS |
| 26 | Kerr et al, Canada | Self-reported HAART adherence | Not reported=1 | Behaviour (1-self-management) | Single item | Adherent or non-adherent, 5-point Likert scale (where 1=occasionally (<25%) and 5=always (100%)) | Moderate predictive validity | HIV-infected patients enrolled in the Vancouver Injection Drug Users Study | Mean age: 40±6.8 | Juxtaposed against pharmacy refill data |

*Continued*
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit or belief) (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates | Juxtaposed against |
|----|-----------------------|--------------------------------------|-----------------------------------------------|-----------------------------------------------|----------------|-------------------------------|-------------------|-----------------------------------------------|------------------|---------------------|
| 27 | Deschamps et al, 2008, Belgium | European HIV Treatment Questionnaire (EHTQ) | Not reported=2 | Behaviour (2- self-management) | 2-item questionnaire on frequency and doses | Non-adherence was defined as (1) adherence: the percentage of doses taken compared with the total doses prescribed and (2) drug holidays: no medication intake for 24 hours+50% of the dosing interval of the medication | Nominal scale; either less than 100% or 1 or more days per 30 days | Poor concurrent validity | HIV-positive adults on antiretroviral therapy followed up at a university hospital | SHCS-AQ and MEMS |
| 28 | Lu et al, 2008, USA | Self-reported antiretroviral adherence questionnaire | I=1, not reported=4 | Behaviour (5- self-management, commitment) | 5-item questionnaire | Adherent or non-adherent | Both nominal scale and rated on 6-point Likert scale where for (1) frequency: 1=none of the time to 6=all the time; (2) percentage of the time were able to take medications exactly as prescribed (0%–100%); (3) ability to take all medications as prescribed (very poor–excellent) | Good convergent and predictive validity | Patients on antiretrovirals from academic medical centres, a community health centre, a general practice based in an academic medical centre and a private infectious diseases practice | Mean age: 42 (SD not available) | MEMS |
| 29 | Kripalani et al, 2009, USA | Adherence to Refills and Medications Scale (ARMS) | I=11, UI=1 | Barrier (7- fill Rx, keep to appointment, inconvenience, cost), Behaviour (3- careless, discipline, ability to follow instruction), Belief (2- stop taking when feeling better or worse) | 12-item scale 2 subscales: (a) adherence to the filling or refilling of prescriptions on schedule; (b) adherence to taking medications | Adherent or non-adherent | 4-point Likert scale where 1=none to 4=all | Good criterion and predictive validity | Patients with CHD attending a primary care clinic | Mean age: 63.7±10.3 | Morisky scale, medication refill adherence and blood pressure measurements |
| 30 | Duggan et al, 2009, USA | Adherence to antiretroviral therapy | I=30 | Barrier (7- storage, physical difficulty, routine), Behaviour (7- support, motivation, self-management), Belief (16 - values placed on antiretrovirals, healthcare providers, knowledge on antiretrovirals, stigma) | 30 items 3 categories of questions: (a) acceptance/avoidance; (b) completely tethered and (c) motivation Have you ever thought having HIV was a ‘punishment’? Do you feel that your medicines are hard to take? Do you believe the medicines for HIV that you take are working for you? | Adherent or non-adherent | Positive/negative-add 1 mark for positive and minus 1 for negative | Good criterion and predictive validity | Patients seeking treatment for HIV infection | Age range: 18–51 | Change in viral load |
| No. | Author, year, country | PROM/scale/rating/ criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|-----|----------------------|--------------------------------------|--------------------------------------|--------------------------------------------------------------------------------|----------------|----------------|----------------|------------------------------------------------|---------------------------------|
| 31  | Gabriel and Violato, 2010, Canada | Antidepressant Adherence Scale (AAS) | 1-3, not reported=1 | Barrier (1- forgetting), Behaviour (1- careless), Belief (2- stopping medications when feeling better/worse) | 4-item questionnaire | High, medium, low adherence | Nominal scale: high-low | Moderate concurrent & predictive validity (adherence level correlated with knowledge and attitude scores); acceptable reliability | Patients treated as outpatients at university hospital following referrals by their family physicians; Mean age: 52±11.6 | Juxtaposed against depression literacy (knowledge and attitudes towards depression and its treatments); 2 instruments completed: MCQ knowledge test of depression and its treatment, and a Likert self-report questionnaire to measure attitudes toward depression and its treatments |
| 32  | Unni et al, 2014, USA | Medication Adherence Reasons Scale (MARS) | 1=15 | Barrier (8- access, challenges in physical dexterity, routine), Behaviour (2- self-management, support), Belief (5- attitude, side effects, number of concurrent medications, healthcare provider trust, treatment efficacy) | 15 items related to medication adherence | Adherent or non-adherent | 5-point Likert scale where 1=none of the time to 5=all of the time | Moderate concurrent & predictive validity; acceptable reliability | Internet users taking cholesterol-lowering medications or asthma maintenance medications or both; Mean age: asthma: 48.7; hypercholesterolaemia: 59.4 | Juxtaposed against MARS |
| 33  | Muller et al, 2015, Germany | Adherence Barrier Questionnaire (ABQ) | 1=14 | Barrier (3- forgetting, challenges, cost), Behaviour (4- careless), Belief (5- stopping medications when feeling better/worse, knowledge) | 14 items | Adherent or non-adherent | 4-point Likert scale where 1=strongly disagree and 4=strongly agree | Good construct validity and reliability | Patients with atrial fibrillation from several general practices - mean age: 72.7±8.3 | Juxtaposed against anticoagulation quality achieved by patients treated with oral anticoagulants |
| 34  | Kleppe et al, 2015, Netherlands | The Probabilistic Medication Adherence Scale (ProMAS) | 1=7, UI=4, not reported=7 | Barrier 2- away from home, Rx refill), Behaviour (1- self-management), Belief (5- trust in doctor) | 18 items | Adherent or non-adherent | Dichotomised scale high-low; yes=0; no=1 | Good discriminant validity and reliability | Elderly receiving medications for chronic conditions recruited by a Dutch agency; Mean age: 68±7.1 | Juxtaposed against MARS |
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years) | SD or IQR, correlates |
|---|---|---|---|---|---|---|---|---|---|---|
| 35 | Sidorkiewicz et al, 2016, France | Sidorkiewicz adherence tool | I=2, not-reported=3 | Barrier (2- holiday/weekends, forgetting), Behaviour (3- self-management, timing careless) | ▶ 5 items ► (a) Early discontinuation of the drug; (b) systematic omission of a daily dose (e.g., at noon); (c) drug holidays; (d) skipping doses and (e) schedule errors | High, good, moderate, poor, very poor adherence | Nominal scale assisted by pictogram; Never to sometimes (6-7 days or more) | Good construct validity and test–retest reliability | Consecutive patients in 6 general practices and 6 care units of university hospitals | ► Consecutive patients in 6 general practices and 6 care units of university hospitals ► Median age (IQR): 59.1 (42.5–70.6) ► Juxtaposed against (1) Liu instrument*; (2) the Adherence Estimator; (3) Physician's rating of patient's adherence; (4) Morisky scale and (5) Treatment Burden Questionnaire |
| 36 | Weinman et al, 2018, UK | Intentional Non-Adherence Scale (INAS) | I=22 | Barrier (3- inconvenience, schedule, cost), Behaviour (1- self-management), Belief (18- knowledge, treatment efficacy, perception, trust in healthcare provider, attitude) | ▶ 22 items on adherence ► E.g., "To see if I really need it," "Because I don't like chemicals in my body," "Because my body is sensitive to the effects of the medicine", "Because I think the drug might become less effective over time" and "Because it reminds me that I have an illness." | Adherent or non-adherent | 5-point Likert scale where 1=strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree | Good construct and moderate predictive validity | Patients from 3 different outpatient clinics (hypertension, oncology and gout) | ► Mean age: hypertension, 66.2; oncology, 62.2; gout, 61.6 ► Juxtaposed against a biomarker measure and with self-reported adherence (BMQ, PAM, BIPQ) |
| 37 | Tan et al, 2019, China | A Chinese and Western medication adherence scale | I=29, UI=2 | Barrier (1-forgotten), Behaviour (4- self-management, careless), Belief (26- knowledge, side effects, dose, stopped taking when feeling better/worse) | ▶ 31 items ► Measures knowledge, belief and behaviour | Higher scores, better the patients' medication adherence. | Nominal scale: MCQ options A-E | Good content and construct validity, excellent internal consistency and test–retest reliability | Patients with CKD who kept long-term follow-up visits to the chronic disease department of a hospital | ► Age range: 18–80 ► Juxtaposed against MGL Scale |
| 38 | Sustersic et al, 2019, France | The Global Adherence Scale for Acute Conditions (GASAC) Questionnaire | I=21, not-reported=3 | Barrier (2- forgetting, Rx refill), Behaviour (3- self-management), Belief (19- felt better/worse, confidence in healthcare providers, system) | ▶ 24 items about adherence – 3 index questions – 21 additional questions on reasons for non-adherence (self, healthcare provider and healthcare system reasons) ► E.g., forgetting, did not refill Rx, issues with treatment regimen, did more harm than good, felt better or worse, confidence in healthcare providers and system | Low, highly adherent | Ordinal scale where 1=not; 2=slightly not; 3=rather yes; 4=yes – final score was expressed as the ratio between 0 and 1 | Good content and construct validity | Patients consulting a hospital emergency department | ► Age range: 21–71 ► Juxtaposed against Girerd questionnaires |

Table 1 Continued
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|--------------------------------------|---------------------------------|---------------------------------------------------------------------------------|-----------------|-------------------------------|-----------------|-----------------------------------------------|--------------------------|
| 39 | Hatah et al, 2020, Malaysia | Malaysia Medication Adherence Assessment Tool (MyMAAT) | I=9, not reported=3 | Barrier (2- Rx refill), Behaviour (6- self-management, social support). Belief (4- did not take when felt better, did not see the significance, fear of side effects, lack of dosing knowledge) | ► 12 items | ► 5 constructs: - Medication-taking behaviour - Perceived utility of medications i.e., benefits, costs and efficacy - Perceived barriers - Perceived self-efficacy and social support - Perceived severity and susceptibility of diabetes | Higher scores indicated better adherence | 5-point Likert scale where 5=strongly disagree to 1=strongly agree | Good content and construct validity; good-excellent reliability | ► Internal consistency, Cronbach's alpha=0.91 |
| 40 | Khabib et al, 2020, UK | My experience of taking medicine (Mymeds) questionnaire | I=13, UI=1 | Barrier (7- refill Rx, forgetting, physical dexterity), Belief (7- did not take when felt better, lack knowledge on dosing and side effects) | ► 14 items | ► 6 sections: current medicines, understanding and satisfaction with medicines, concerns about medicines, practical barriers, filling medicines into daily routine and adherence to secondary prevention medicine over the past month | Adherent or non-adherent | 5-point Likert scale for how often each medicine was taken as prescribed in the past month (all of the time; nearly all of the time; most of the time; about half the time; less than half the time) | Good face validity | ► Internal consistency, Cronbach's alpha=0.71 |
| 41 | Goh et al, 2020, Malaysia | Patient-Medication Adherence Instrument (P-MAI) and a Healthcare Professional-Medication Adherence Instrument (H-MAI) | I=24, not reported=2 | Barrier (13- routine, forgetting, Rx refill, cost, other coexisting conditions, missed appointments, lack of privacy, confused about instructions), Belief (10- knowledge, relationship with healthcare provider, dosing, stopped taking when feeling better/worse, efficacy) | ► 26 items on patient-reported adherence (P-MAI-9) | ► 8 items: knowledge/ belief.7 items and reasons for not taking medications as directed for the past 2 weeks=17 items | Higher score indicates better adherence | 5-point Likert scale where 1=strongly disagree to 5=strongly agree | Good content and construct validity | ► Internal consistency, Cronbach's alpha=0.72 |
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain; barriers (practical), behaviour (habit) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|--------------------------------------|-----------------------------------|-----------------------------------------------|----------------|---------------------------------|-----------------|-----------------------------------------------|-----------------------------------------------|
| 42 | Haag et al, 2021, Switzerland⁵⁶ | Barriers to Oral short-Term antibiotic Adherence (BIOTICA) | I=15 | Barrier (4- difficulty to swallow, forgetting, difficult to incorporate in daily life, no support from care giver), Behaviour (3 - no intention to take/intend to miss a dose), Belief (8- side effect/interactions, knowledge, unnecessary, unfamiliar with consequence, no trust in prescriber, information could not be understood / insufficient) | 15 items | Barrier-items were in 10 of 11 theoretical domain framework and included environmental context and resources, knowledge, social influence, emotions, beliefs about capabilities Intentions, memory, skills, beliefs about consequences and social, professional role and identity | Higher scores indicated higher degree of non-adherence | 5-point Likert scale where 1=strongly disagree to 5=strongly agree | Good content and construct validity, Cronbach’s alpha=0.72, item correlation >0.2 (acceptable) | Patients assessed before antibiotic initiation in the outpatient setting (pharmacies and surgeries) | Mean age 51.5±16.7 (range: 19–85 years) Juxtaposed against pill count by MEMS REDCap |
| 43 | De Las Cuevas et al, 2021, Spain⁵⁷ | Patient Health Beliefs Questionnaire on Psychiatric Treatment | I=8 | Belief (8- side effect/interactions, knowledge, unnecessary, unfamiliar with consequence, no trust in prescriber, information could not be understood / insufficient) | 17-item self-reported health beliefs scale. 2 subcales (9 items) were related to medications: Negative aspects of medication (pharmacophobia) Positive aspects of medication (pharmacophilia) | Higher scores on each subscale indicate a stronger belief towards psychotropic treatment | 6-point Likert scale where 1=totally disagree, 6=totally agree | Good construct validity and reliability | Outpatients with schizophrenia and other psychiatric conditions | Mean age 41.2±12 (n=212 for schizophrenia) and 44.5±14 (n=1160 for other mental disorders) Juxtaposed against Sidorkiewicz Adherence Tool |
| 44 | Seyma and Buyasal, 2022, Turkey⁵⁸ | Scale for Compliance to the Treatment in Type II Diabetes Mellitus | I=7 | Behaviour (9- anxious when time for insulin, schedules, medication intake, take regularly), Belief (4- knowledge on DM, consequence of condition, trust in healthcare, diet over medication) | 30-item self-reported adherence to type 2 DM treatment | Good, moderate, poor adherence | 5-point Likert scale where 1=strongly agree, 5=strongly disagree | Good content and construct validity, Cronbach’s alpha=0.7 | Patients with DM presenting to the Internal Diseases and Endocrinology clinics of a hospital | Mean age 54.6±9.5 Juxtaposed against Diabetes Health Literacy Scale |

Number of measures, n=44 of 59; Intentional, I items=491; Unintentional, UI items=35. Not reported=67 items. For a measure to be classified as Intentional, >30% of its items are to be Intentional. *All terms related to adherence, e.g., patient-reported outcome measures; PROMs, patient-reported adherence to medication scale; VAS, Visual Analogue Scale. Some values were reported as median, range or not reported.
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (physical/practical), behaviour (act) or belief (perception) | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|------------------------|--------------------------------------|------------------------------------------|---------------------------------------------------------------------------------|-----------------------------|-----------------|---------------------------------------------------|-----------------------------------------------|
| 1  | Brooks et al, 1994, USA | Brooks Medication Adherence Scale (BMAS) | I=8, UI=4 | Barrier (1- forgetting), Behaviour (1- careless), Belief (10- stopping/after medications when feeling better/worse/due to adverse effect/lack of efficacy) | High, medium, low adherence—whether patients took their medicine or used their inhaler at the prescribed times and in the prescribed amount | Dichotomised scale high—low yes=0; no=1 | Good discriminant validity and reliability Internal consistency, Cronbach’s alpha=0.93 | Pulmonary disease clinics 47% aged 50 or older Juxtaposed against physician rating of asthma severity |
| 2  | Kim et al, 2000, USA  | Hill-Bone Compliance to High Blood Pressure Therapy Scale | I=4, UI=2 | Barrier (4- Rx refill, forgetting, miss appointments), Behaviour (1- careless), Belief (1- stopping when feeling better or worse) | Adherent or non-adherent 4-point Likert scale (where 4=all the time, 3=most of the time, 2=some of the time and 1=never) Total scores=14–56 | Good content, construct and predictive reliability Internal consistency, Cronbach’s alpha=0.74 | Adults with hypertension enrolled in 2 separate clinical trials Mean age (trial 1)=41.3±5.3 Mean age (trial 2)=59.2±13.1 |
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (physical/practical), behaviour (act) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age * (years)±SD or IQR, correlates |
|----|-----------------------|--------------------------------------|---------------------------------|----------------------------------------|----------------|-------------------------------|------------------|---------------------------------|-----------------------------------------------|
| 3  | Lewis and Abell, 2000, USA<sup>14</sup> | Adherence Attitude Inventory (AAI) | I=16, UI=12 | Barrier (12), Behaviour (8), Belief (8) | ► 28-item questionnaire | Adherent or non-adherent | 7-point Likert scale (ranging from none of the time to all of the time) | Good content and construct validity, good to acceptable reliability | Clients of AIDS service organisations and/or medical centres |
|    |                       |                                      |                                | E.g., forgetting to take, to refill prescriptions, forget to inform doctor about adverse effect, involvement of healthcare provider to assist adherence, fear of keeping to schedule, self-doubt, self-management, commitment |                                |                               |                                | ► Internal consistency, Cronbach’s alpha between 0.85 and 0.95 | Mean age: 41±8.8 |
|    |                       |                                      |                                | - In the afternoon, I have a hard time remembering if I took my early dose of medication. |                                |                               |                                | ► Juxtaposed against Multidimensional Quality of Life for Persons with HIV/AIDS and the General Perceived Self-Efficacy Scale | |
|    |                       |                                      |                                | - Even though I want to take my medication, I just forget to take it. |                                |                               |                                |                                | |
|    |                       |                                      |                                | - My medical provider wants me to participate in making decisions about my medicine. |                                |                               |                                |                                | |
|    |                       |                                      |                                | - Things get in the way of my taking my medication as prescribed. |                                |                               |                                |                                | |
|    |                       |                                      |                                | - I am committed to taking my medication even if it tastes bad or is hard to swallow |                                |                               |                                |                                | |

Continued
Table 2 Continued

| No | Author, year, country | PROM/scale/rating/criteria/instrument                                                                 | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (physical/practical), behaviour (act) or belief (perception) | Item construct                                                                 | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age (years)±SD or IQR, correlates                                                                 |
|----|-----------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|------------------------------|-----------------|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
| 4  | Ziegelmann et al, 2002, UK | Transplant Effects Questionnaire (TxEQ)                                                                 | I=2, UI=2, not reported=1                                                      | Barrier (3), Behaviour (1), Belief (1)                                                              | ► 5 items related to medication-taking conduct as part of 24 items             | Adherent or non-adherent        | 5-point Likert scale (ranging from strongly disagree to strongly agree) | Content validity established, acceptable reliability                                                                 | Patients registered at a teaching hospital                                                                 |
|    |                       |                                                                                                        |                                                                                | E.g., do not take, sometimes forget to take, forget to take when busy, sometimes think do not need, find it difficult to adjust to taking, anti-rejection medicines |                                                                                   |                             |                              | Internal consistency, Cronbach’s alpha=0.79                                                                 | Mean age: 45.2±14.5                                                                                         |
|    |                       |                                                                                                        |                                                                                |                                                                                                  |                                                                                   |                              |                              | Juxtaposed against self-efficacy                                                                             |                                                                                                              |
| 5  | Knobel et al, 2002, Spain | Simplified Medication Adherence Questionnaire (SMAQ)                                                   | I=2, UI=2, not reported=2                                                      | Barrier (4), Behaviour (1), Belief (1)                                                              | ► 6-item questionnaire                                                       | Adherent or non-adherent        | Dichotomised scale: yes=0; no=1                           | Content, concurrent and predictive validity established, good reliability                                   | HIV-infected patients from 69 multicentres or hospitals                                                   |
|    |                       |                                                                                                        |                                                                                | E.g., forget, careless, stop taking if feel worse, did not take over the past weekend, how many days did not take any medicine at all over the past 3 months |                                                                                   |                             |                              | Internal consistency, Cronbach’s alpha=0.75                                                                 | Mean age: 35.8±7.9                                                                                         |
|    |                       |                                                                                                        |                                                                                |                                                                                                  |                                                                                   |                              |                              | Juxtaposed against MEMS                                                                                     |                                                                                                              |
| 6  | Greaves et al, 2005, UK  | Patterns of Asthma Medication Use Questionnaire                                                       | I=3, UI=2, not reported=1                                                      | Barrier (2- forgetting, ADL/routine), Behaviour (2- careless, self-efficacy), Belief (2- lesser dose, stopped when feeling better) | ► 6-item questionnaire                                                       | Adherent or non-adherent        | Response coded into 4 categories: (1) regular=patients who take their medication regularly; (2) forgetting-those who forgot on two or more occasions per week, (3) low dosing-those who took medication regularly but at a reduced amount, (4) symptom directed-those who varied their strategy in response to symptom levels, in some cases stopping completely | Good criterion and construct validity                                                                            | Unscheduled asthma care visits and quality of life for adherent and non-adherent patient groups from a seminurals GP practice |
|    |                       |                                                                                                        |                                                                                | E.g., forgetting frequency and main reason for not taking, take regularly but less than recommended, decide each day whether to use it, depending on how I feel, stop taking when feeling better |                                                                                   |                             |                              |                                                                                                              | Mean age: 42.1±10.6                                                                                         |
|    |                       |                                                                                                        |                                                                                |                                                                                                  |                                                                                   |                              |                              |                                                                                                              | Age range: 21-61                                                                                          |
|    |                       |                                                                                                        |                                                                                |                                                                                                  |                                                                                   |                              |                              |                                                                                                              | Juxtaposed against pharmacy records and clinical outcome (asthma)                                          |
| No | Author, year, country | PRM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items & (I, UI, not reported) | Process measure, item domain: barriers (physical/practical), behaviour (act or belief) (perception) | Classification of non-adherence | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|---|---|---|---|---|---|---|---|
| 7 Schroeder et al, 2006, UK<sup>22</sup> | Adherence Self-Report Questionnaire (ASRQ) | I=2 (I always take at the same time)† I/UI=3 (knowingly/unknowingly, not reported)=1 (I hardly take any medication) | Behaviour (6- self-management) 6 items on adherence 6. E.g., miss taking at specific times, knowingly or unknowingly | Adherent or non-adherent 6-point Likert scale where 1=perfect and 6=low | Good content validity, moderate predictive validity | Patients with uncontrolled hypertension from GP practices enrolled in an RCT  Mean age: 67.9±10.3  Juxtaposed against MEMS |
| 8 Muñoz-Moreno et al, 2007, Spain<sup>23</sup> | Self-Report Adherence Questionnaire (SERAD) | I=1, UI=1 | Behaviour (1- discipline) 6- not having the medication on time 6. for the reason for non-adherence, choose, either - Barrier  - Simply forget, routine, holidays/weekend, clash with other medications, presence of others not within CoC, refill Rx OR - Belief (1): † Atitude, adverse events, not willing, misunderstanding with prescription/prescriber | 2 items 2. 2 types of indexes: - number of times the patient failed to take the medication (adherence percentage) - number of times the patient failed to observe the intake conditions (intake conditions observed percentage). specifies any of the 13 reasons for non-adherence | Nominal scale 1. Adherence with regard to the doses missed during the last week, last month and last 3 months, % 2. Reasons for non-adherence during the last week, last month and last 3 months, % 3. Adherence with regard to the times that intake conditions were not observed during the last week, % 4. Reasons for intake conditions not observed during the last week, last month and last 3 months | Good concurrent validity | HIV-infected outpatients  Mean age: 38±10  Juxtaposed against pill count, plasma level, MEMS |
| 9 Chesney et al, 2000, USA<sup>24</sup> | Adult AIDS Clinical Trials Group (AACTG) Adherence Instrument | I=6, UI=6, not reported=5 | Barrier (6- ADL/routine affected), Behaviour (7- self-management, motivation), Belief (4- stopping medications when feeling better/worse) | 17-item questionnaire 2. 2 sets: Adherence to Anti-Retroviral Medications and ‘Baseline Correlates of Adherence’ - 5 items on recent and distal adherence (missed doses) - 12 items on reasons for missed dose | Adherent or non-adherent Rated on 4-point Likert scale (where 4=never, 3=sometimes and 1=often) | Excellent reliability, good content, convergent and predictive (construct) validity | Patients enrolled in 10 AIDS Clinical Trials Units in the USA  Mean age: 39 (range: 20–72)  Juxtaposed against pill count, plasma level, MEMS |
| No | Author, year, country | PROM/scale/rating/criteria/instrument | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (physcial/ practical), behaviour (act) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|--------------------------------------|-----------------------------------------------|----------------------------------------------------------|----------------|-------------------------------|------------------|-----------------------------------------------|---------------------------------------------|
| 10 | Fernandez et al, 2008, USA | Medication Adherence Self-Efficacy Scale-Revision (MASES-R) | I=8, UI=6 | Barrier (8- challenging situations, e.g., busy, when travelling, holiday), Behaviour (1- self-management), Belief (4- stop taking when feeling better) | 13-item questionnaire | Adherent or non-adherent | 4-point Likert scale where 1=not at all sure to 4=extremely sure | Good predictive validity | Hypertensives attending primary care practices<br>Hypertensives attending primary care practices<br>Mean age: 54±12.4 | Juxtaposed against MEMS |
| 11 | Hahn et al, 2008, USA | Adherence Starts with Knowledge-20 (ASK-20) | I=12, UI=8 | Barrier (8- refill Rx, forgetting, challenges like hard to swallow, closing, cost), Behaviour (1- lack of support), Belief (11- dosing, trust in healthcare provider, medicine didn’t work) | 20-item questionnaire | Adherent or non-adherent | 5-point Likert scale ranging from ‘strongly agree’ to ‘strongly disagree’ or from ‘in the last week’ to ‘never’ | Good concurrent validity | Patients on medications for asthma, depression and diabetes<br>Mean age: 52.5±13.8 | Juxtaposed against self-reported adherence |
| 12 | Turcu-Stiolica et al, 2021, Romania | Adherence to Direct-Acting Agents for Hepatitis C Virus (HCV-AD) | I=7, UI=3 | Barrier (1- no stock), Behaviour (3- skipped, forgot, not daily), Belief (6- side effects, not sure works, too many, fear of addiction, feeling better/worse, not a miracle) | 10-item questionnaire | Adherent or non-adherent | 5-point Likert scale ranging from ‘strongly disagree’ to ‘strongly agree’ or from ‘never’ to ‘very often’ | Good concurrent validity and content validity | Patients at a hospital’s gastroenterology department taking direct-acting antivirals for HCV infection<br>Mean age: 60.8±12.1 | Juxtaposed against VAS and MPR |
| No | Author, year, country | Outcome measure, number of intentional or unintentional items (I, UI, not reported) | Process measure, item domain: barriers (physical/practical), behaviour (act) or belief (perception) | Item construct | Classification of non-adherence | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age* (years)±SD or IQR, correlates |
|----|-----------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------|-------------------------------|-----------------|------------------------------------------------|---------------------------------|
| 13 | Silveira et al., 2021, Brazil[87] | Treatment Adherence Measure of Immunomodulators for Patients with Multiple Myeloma | Behaviour (2- forgot, careless), Belief (5- feeling better/worse, interrupted treatment) | 7-item questionnaire, E.g., careless, forgot, feeling better/sick | Adherent or non-adherent | 5-point Likert scale ranging from 'always' to 'never' | Construct and convergent validity established | Patients at outpatient clinics, diagnosed with myeloma and treated with an immunomodulator for at least 1 month; Median age (IQR): 62.7 years (14.4) | Juxtaposed against Quality of Life Questionnaire Core and the Quality of Life Questionnaire Multiple Myeloma module |

Number of measures, n=13 of 59; Intentional, I=79, Unintentional, UI=50. Not reported=9 items; for a measure to be classified as mixed, a balanced of I and UI items are to be present i.e., >30% items I; >30% items UI.

*Some values were reported as median, range or not reported.

†When item specifies both I and UI (e.g., "knowingly or unknowingly", did you forget?), the item is categorised as Intentional (healthcare professional to assess further whether a more serious intervention is needed or recommending methods to improve habit would suffice).

‡When a patient is expected to choose one answer from barrier OR belief, the item is categorised as belief (a domain which can have targeted intervention by healthcare professionals); Barrier=56, Belief=54, Behaviour=28 items.

ADL, activities of daily living; CoC, Circle of Confidentiality; GP, general practitioner; MEMS, medication event monitoring system; MPR, medication possession ratio; PROMs, patient-reported outcome measures; RCT, randomised controlled trial; Rx, Prescription; SD, standard deviation; VAS, Visual Analogue Scale.
### Table 3  PROMs of unintentional (UI) non-adherence—n=2 of 59 measures, 9 items

| No | Author, year, country | PROM/scale / rating/ criteria/instrument | Outcome measure, number of UI, intentional (I), not reported items | Process measure, item domain: barriers (physcial/practical), behaviour (act) or belief (perception) | Item construct | Classification of non-adherence* | Method of scoring | Psychometric properties, (reliability and/or validity) | Setting, age (years)±SD, correlates |
|----|------------------------|----------------------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------|---------------|---------------------------------|-----------------|---------------------------------|----------------------------------|
| 1  | Fodor et al, 2005, Hungary | Adherence Questionnaire                | UI=3, I=1                                                      | Behaviour (3 self-management, careless), Belief (1)                                           | 8th of 9 items; 8th item has 4 subquestions  E.g., patient's self-efficacy, self-management (occasionally forget, sometimes forget, frequently forget, or decide not to take for short or extended period) | Adherent or non-adherent  Patients who claimed to be taking medications every day were classified as adherent | Dichotomised scale: yes=0; no=1 | Good determinant validity, no report on reliability | Hypertensives among blue collar employees in 3 central European countries: Austria, Hungary and Slovakia during work site screening for hypertension  Mean age: 48.9±7.4 in the adherent group and 46.7±8.9 in the non-adherent group  Juxtaposed against blood pressure control |
| 2  | Chisholm et al, 2005, USA | Immunosuppressive Therapy Adherence Instrument (ITAS) | UI=2, I=1, not reported=2                                      | Barrier (1-forget), Behaviour (2 careless, self-management), Belief (2 stop when feeling better or worse) | 5-item questionnaire  E.g., how often: 'forgot to take, careless about taking, stop because you felt worse and miss …for any reason' | Adherent or non-adherent  Non adherence defined as not taking their ciclosporin or tacrolimus as advised/prescribed over a 3-month time period given a particular circumstance | A=0% of the time (none), B=1%-20% of the time, C=21%-50% of the time and D=>50% of the time | Moderate construct and concurrent validity, good reliability  Internal consistency, Cronbach's alpha=0.81 | Organ transplant recipients  Mean age: 52.2±14.1  Juxtaposed against refill record, adherence rates, serum immunosuppressant concentrations, graft rejection and increased serum creatinine levels |

Number of measures, n=2 of 59; Unintentional, UI items=5, Intentional, I items=2, Not reported=2 items; for a measure to be classified as Unintentional, >30% of its items are t be Unintentional and the remainder Intentional and/or Not reported (if any).  
*All terms related to adherence, E.g., compliance is standardised and reported as adherence; Behaviour=5, Belief=3, Barrier=1 item(s). BP, blood pressure; NA, not applicable; PROMs, patient-reported outcome measures; SD, standard deviation.
Associations between PROMs increasing propensity to detect an intentional non-adherence outcome and type of patient care, and the process domains

| Type of patient care—primary care (general practice, community pharmacy and optometry versus specialised care) | Belief criterion items | Barrier criterion items | Behaviour criterion items |
|---------------------------------------------------------------|------------------------|-------------------------|---------------------------|
| OR 95% CI P value                                              | Standardised beta P value | Standardised beta P value | Standardised beta P value |
| Increase in the detection of intentional non-adherence        | *1.9 1.01 to 2.66 0.044  | *0.79 <0.001             | *0.34 <0.001              | 0.087 0.62 |

*p<0.05.

PROMs, patient-reported outcome measures.

table 3—unintentional, UI (n=2 of 59 instruments). Of the total 572 intentional criterion items, I=491, I=79, and I=2 were split into the intentional, mixed intentional/unintentional, and in the unintentional categories, respectively. Of the total 90 unintentional criterion items, UI=35, UI=50, and UI=5 were split into the intentional, mixed intentional/unintentional, and in the unintentional categories, respectively. Finally, additional n=67, 9 and 2 items were not reported within each category.

Process measures

The process domains which affected non-adherence were belief (383 items), barrier (192 items) and behaviour (165 items).

Correlation and regression analyses

There was a strong positive correlation between the outcome domain, intentional (I) and the process domains, belief (Spearman’s ρ=0.88, p<0.001) and barrier (Spearman’s ρ=0.59, p<0.001), i.e., the numbers of belief and barrier criterion items increased, along with the numbers of intentional criterion items.

The results of the regression analyses are displayed in table 4. Regression models were adjusted for respondents’ age. There was a positive and significant association between increased PROMs’ propensity to detect intentional non-adherence and primary care (vs specialised care) that patients received (OR=1.9; 95% CI=1.01 to 2.66), i.e., a measure was 1.9 times more likely to have detected an intentional non-adherence event among patients who attended primary care as compared to those attending secondary and tertiary care appointments, or who were hospitalised at these facilities. Similar findings were obtained for negative beliefs and barriers encountered. For every belief or barrier criterion item included, the PROMs’ aptitude for detecting intentional non-adherence increased by β=0.79 and β=0.34 units, respectively. Model R²=0.94, i.e., 94% of variance in the outcome variable intentional non-adherence can be explained by the predictor variables belief and barrier.

PROM characteristics

Psychometric properties

All studies included had a minimum of two psychometric properties assessed and described (online supplemental appendices 6–8). With reference to validity, hypotheses testing for content (including face) validity and/or construct validity were evaluated in a majority of the studies. With reference to reliability, the parameter internal consistency, was evaluated in 38 studies, respectively. Measurement error or cross-cultural validity/measurement invariance was not evaluated in any of the studies. In addition, many of the studies assessed PROMs’ development, but they were not necessarily of good methodological quality (for example, limited information on data validity as described in the eligibility section) and were hence excluded.

Defining and scoring adherence

There was heterogeneity in the term ‘adherence’ used in the studies. First, this was evidenced in the cut-off points used for determining level of non-adherence, for example, ‘habitual to occasional refusers of medications’, ‘high, medium or low adherence’, and ‘adherent’ or ‘non-adherent’. All PROMs that had a component of unintentional had binomial categories of ‘adherent’ versus ‘non-adherent’. While a handful of studies specified the score which determined ‘high’ score and hence ‘highly’ adherent, others reported that a higher score indicated better adherence. A majority of the measures (n=47 of 59 instruments) were worded as closed-ended questions and provided responses in the form of nominal or Likert scales; seven measures were open-ended and provided dichotomised Yes/No scale (which ultimately yielded a positive or negative overall score which determined level of adherence).

Several measures incorporated an addition of Visual Analogue Scales (VAS). The measures for assessing adherence were patient or interviewer-administered and conducted via face-to-face interviews (real-time or virtual), telephone interviews, questionnaires, diaries or internet surveys.
Extent of non-adherence

Seven measures specified a time period for non-adherence, for example, ‘Did you miss a tablet—yesterday? last week? last month? or in the last 3 months?’ Fifteen adherence measures specified a frequency for skipping or missing doses, for example, ‘How many days over the past month did you take less than prescribed?’ The time frame specified ranged from 1 day to 12 months. Most of the items were interpreted from measures that state the number/amount of doses taken compared with those prescribed for that time period. Haag et al went on to stratify their analysis according to level of adherence for daily, two times per day and three times a day regimen.

Disease-specific measures

Some of these adherence scales are disease-specific and thus explored common predictors that may influence adherence in those diseased populations. Examples of diseases or statuses explored were asthma,51 diabetes, AIDS,58 hypertension,57 chronic diseases, acute osteoporosis, eye-related conditions,16 cardiovascular, and organ transplant recipients.97,98

DISCUSSION

Quantification of adherence and non-adherence

Medication adherence has been defined as ‘the extent to which patients take medications as prescribed by their healthcare providers’,71 while its measurement is the process of systematically assigning numbers or words to tangible and intangible characteristics so that they can be defined, quantified and differentiated. In our review of 59 PROMs, these self-reported measures aimed at quantifying medication adherence based on the responses from a nominal or Likert-point scale and assigning categories to the total scores. A small number of adherence measures had taken a different approach to assigning the ‘adherent’ category. The Medication Adherence Questionnaire (MAQ), Morisky Medication Adherence Scale (MMAS), Brief Medication Questionnaire, Adherence Self-Report Questionnaire (ASRQ) and VAS categorised patients into levels of adherence. For example, the MAQ and MMAS categorised the population into high, medium and low levels of adherence whilst several others collectively grouped respondents with medium and low adherence scores into a broader ‘non-adherent’ class. For the Brief Medication Questionnaire, the study population was grouped into repeat, sporadic and no non-adherence. The ASRQ and VAS classified non-adherence into six and seven levels, respectively, based on the researchers’ expertise. Where reported, the most common cut-off point for non-adherence is the score below the corresponding point of another objective or self-reported measure. For instance, the cut-off was the point where it was revealed that the patients took 80% of their medication. The MMAS cut-off points, for instance, were selected based on the correlation with blood pressure control. Other adherence measures, such as the Drug Attitude Inventory, Adherence Attitude Inventory and Medication Adherence Self-Efficacy Scale-Revision first segregated the population into adherent and non-adherent based on responses to questions about whether medications were taken or not, and then compared the mean scores of the two adherence measures to determine the cut-off.

Psychometric properties

Since the publication of the inaugural study on adherence in 1968,72 many studies aimed at understanding factors related to poor adherence, yet they lacked crucial perspectives on the measurement tools used to evaluate non-adherence. The approach for combining adherence and its measurement is complex given that adherence impacts health-related clinical outcomes.73 The analyses of PROMs’ psychometric properties were hence essential, given the vast and multidimensional outcomes they evaluated. To ensure construct validity, several studies used exploratory factor analysis to ascertain that the smallest number of factors that best represented the items was retained.27 42 50 Reliability was evaluated using Cronbach’s alpha tests for internal consistency to assess how closely related a set of items were as a group and this was frequently reported and often yielded values of more than 0.7, indicating a relatively acceptable level of internal consistency and correlation between PROM items. In addition, the reliability of a measurement tool in consistently reproducing the same result across several measurements, denoted using a test/retest reliability score, were also not regularly reported.

It is crucial to evaluate PROM in the context of evaluating medication-taking conduct, i.e., its construct and structure need to be sensitive and adequately detect aspects of medication-taking behaviour. Medication-taking behaviours were often detected when using a direct, indirect or a combined method. The most precise approaches were postulated to have been direct methods, such as directly observed therapy, biological methods, and measurement of the level of medicine or metabolite, for example, blood or urine drug concentrations. Numerous indirect methods were equally proposed, such as the use of clinician reports, data from rates of prescription refills, pill counts, electronic medication monitors, patient diaries and patient self-report measures as well as healthcare provider-reported measures. When reporting on aspects of PROMs’ construct, many of the studies evaluated its criterion and/or discriminant validity. However, there is also a school of thought that described criterion validity as being inaccessible for evaluation as it requires a component of comparison with an established ‘gold’ standard. The authors synthesised the studies and deemed proxy measures as either direct, indirect or a combination of both, as standards against which the PROMs were validated.

In summary, the review identified 59 unique PROMs of medication adherence. The selected 59 PROMs demonstrated ease of administration primarily in community
dwellers seeking services at primary healthcare facilities. Patients who visited secondary or tertiary care outpatient clinics, blue collar workers undergoing health screening and patients hospitalised following emergency department visits were end-users of the PROMs. These measures were tested primarily on adherence to pharmacotherapy for psychiatric disorders, and for retroviral and cardiovascular diseases. This was an indication that the PROMs had good usability and credibility, and were meaningful to be used for their targeted populations. Eight of these outcome measures had adequate, evidence-based psychometric properties, and had the aptitude to identify those who intentionally failed to adhere to good medication-taking conduct. They were the Compliance Questionnaire Rheumatology,\textsuperscript{22} Immunosuppressant Therapy Barrier Scale,\textsuperscript{27} Medication Adherence Rating Scale,\textsuperscript{20} Treatment Satisfaction Questionnaire for Medication,\textsuperscript{25} Self-Efficacy for Appropriate Medication Use Scale,\textsuperscript{32} Medication Adherence Assessment Tool,\textsuperscript{50} Patient-Medication Adherence Instrument and Healthcare Professional-Medication Adherence Instrument\textsuperscript{52} and Barriers to Oral short-Term antibiotic Adherence\textsuperscript{53} questionnaires. Two measures with adequate, evidence-based psychometric properties had the aptitude to identify those who intentionally and unintentionally failed to adhere to good medication-taking conduct. They were the Adherence Starts with Knowledge-20\textsuperscript{66} and Hill-Bone Scale\textsuperscript{37} questionnaires.

\textbf{Intentionality (intentional and/or unintentional)}

While the advantages of those psychometric properties were recognised, authors seldom weighed in on the inherent ability of self-reports to assess intentionality. A patient’s belief, past experiences and cognition level may equally come into play, influencing medication-taking conduct. Decisions by patients may be well-informed or ill-informed driven by concerns over the benefits and risks of their medication.\textsuperscript{74} Using theories of Planned Behaviour and the Common Sense Self-regulatory Model of Illness, several attempts were made to explain variation in adherence to medication.\textsuperscript{17} A social cognition model that aims to explain one’s intentional non-adherent conduct was developed in 1999 by Horne\textsuperscript{17} and was founded on the Health Belief Model\textsuperscript{75} and the Illness Perceptions Model.\textsuperscript{76} According to Horne, adherence to medication is based on patients’ deeply-rooted belief concerning perceived severity of illnesses, i.e., perceptions and their understandings, and hence, knowledge of the nature of the illness, and treatability.\textsuperscript{17} In the context of adherence, belief is usually associated with intentional non-adherence because the belief can strongly lead to an active decision either to follow or not to follow instructions by healthcare professionals.

Self-efficacy, on the contrary, is key for habitual non-adherence and is a term that encompasses self-management skills, discipline and the state of being self-sufficient.\textsuperscript{77 78} In our review, we observed more of such terms in the later versions of the health beliefs model to increase the explanatory power of the theory, placing emphasis on patient accountability.\textsuperscript{79 80} In recent times, during the COVID-19 pandemic, the health promotion model is also referenced to as it emphasises self-efficacy and purports that judgement about one’s ability to successfully perform challenging tasks is based on four types of criteria: (a) behavioural engagement and evaluating performance, (b) observation of how others perform, (c) verbal persuasion by others about one’s ability, and (d) anxiety, fear, calm, tranquillity, or other physiological states associated with self-judgement of competencies.\textsuperscript{81 82}

When used effectively, measurement tools such as self-reports essentially screen for these predictors (be it one’s belief system—perceptions, experiences, knowledge and trust towards healthcare professionals or one’s behaviours—self-efficacy and habits). These perspectives are important for better understanding of the underlying reasons contributing to non-adherence. As this review demonstrates, distinguishing intentional from unintentional non-adherence is pertinent. Only then can appropriate and targeted interventions be provided to the patient.\textsuperscript{73 83}

\textbf{Limitations}

Although we successfully classified each item of every measure or instrument based on intentionality for non-adherence, future research using a similar approach may reveal varied findings. This is because the process of classification was largely dependent to a certain extent, on one’s interpretation of the criterion items’ construct and thereby the consequences of treatment default. Our findings also cannot be used to ascertain the phase of medication taking, whether ‘initial, i.e., starting a recommended medication regimen’, or ‘implementation, i.e., executing the prescribed dosage schedule’ or ‘persistence, i.e., length of time on regimen before discontinuation’.\textsuperscript{84} In addition, while there is a body of evidence to suggest that past negative experiences with the healthcare systems were attributed to the intention to default treatment, the key role of healthcare professionals in advocating positive habits for medication adherence remains vital. In other words, past negative experiences could become positive and the new experience should equally influence medication-taking conduct.

\textbf{Recommendations for best practice}

Many of the studies identified PROMs of adherence towards antiretroviral and post-organ transplant therapies. End-users of these measures can easily be subjected to stigmatisation, and as such, undergoing a series of validity tests including cross-cultural validity, can prove beneficial for the development of individual measure items. This is also true for measures where the appeal, social desirability and sensitivity are of concern, and yet the assessment needs to be conducted without compromising the method in which the latent trait of the measure is being measured across cultures and populations. For instance, as proposed by Stirratt et al.,\textsuperscript{84} respondents with cognitive impairment may require other approaches such as daily
texts, interactive voice response surveys, or computer-assisted measures.

In addition, the testing for criterion and construct validity was often conducted using proxy measures as opposed to direct measures. Although our review demonstrated the link between intentional non-adherence and one’s belief system, and in theory, responses to sociocognitive domains can be used as proxy measures, we recommend further statistical analyses, for example sensitivity and positive predictive value calculations, to assess the concordance of direct and proxy measures of individual measure items. Despite having the advantage of producing quick results, a PROM needs to be reliable, its results reproducible, and have an ability to capture a single underlying aspect of behaviour, barrier, or belief, and map that construct onto a valid measurement scale.

Our findings demonstrated that existing measures had sufficient evidence-base and psychometric properties, and therefore, should first be used, as opposed to developing a new measure, unless the study subjects do not correspond with the tested population.65 Consensus of a panel of experts is necessary for determining criteria for scoring and cut-off for adherence versus non-adherence. They need to consider frequency and dose (and the allowable deviation in the amount prescribed whenever the patient decides to lower or increase dose), as well as determine habitual versus occasional refusers. Additionally, developing response items that differentiate adherence in ordinal terms (e.g., anchored Likert rating scale), nominal or VAS (e.g., estimated level of doses taken) may help decrease ceiling effects. To curb recall bias, phrases like ‘during the last weekend’ and ‘in the past 7 days (to include one weekend)’ were preferred. A 30-day recall period, as opposed to brief intervals, can also be considered in view of its advantageous impact on ceiling effect reduction.

Finally, future research could underscore the adjudication of measurement errors and their sources of variability, as there is a paucity of information in these areas. Elucidating responsiveness of PROMs and their ability to detect changes in clinical conditions of patients are also potential areas for psychometric characteristic evaluation.

CONCLUSION

The data spanning four decades revealed that PROMs were developed to assess medication non-adherence, which had increasingly become more intentional. Of the 59 studies, ten PROMs had adequate, evidence-based psychometric properties. Of the ten, eight and two PROMs were able to detect total and partial intentionality to medication default, respectively. Measures with matching intentionality properties will better detect non-adherence, thereby relieving clinicians from having to contemplate on ineffective medications or therapeutic failure due to drug resistance. Finally, recommendations for patients to simply use daily reminders to consume medication should be brought to a halt as it seems counterintuitive to tackle the premeditated intentional non-adherence. Instead, because our data demonstrated a link between intentional non-adherence and one’s belief, empowering patients with the appropriate knowledge, helping them to better manage their illnesses, and strengthening their trust in medications and healthcare providers could be more reliable impetuses to drive positive attitudes and perceptions. However, these need to commence at the primary care level.

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