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Title page

Title: Development and validation of a self-report measure of practical barriers to medication adherence – the Medication Practical barriers to Adherence Questionnaire (MPRAQ)

Running head: Practicalities measure (MPRAQ)

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Abstract (250 words)

Aim: This study reports the development and validation of a new self-report measure (MPRAQ) that assesses practical barriers to medication adherence.

Methods: MPRAQ comprises fifteen statements describing practical barriers. Responses are scored on a 5-point Likert scale; higher scores indicate more practical barriers. Initial face validity was evaluated by cognitive testing with patients from a diabetes support group. Following refinement, internal reliability and construct validity were assessed in two samples: patients recruited via Amazon mTurk and the Nivel Dutch Healthcare Consumer Panel (COPA). Respondents completed the Beliefs about Medicines Questionnaire (BMQ – general and specific), and Medication Adherence Report Scale (MARS-5). The mTurk sample also completed the Perceived Sensitivity to Medicines questionnaire (PSM), and repeated MPRAQ two weeks later to assess test-retest reliability.

Results: Face validity was evaluated in 15 patients (46% female; mean(SD) age 64(12) years). A total of 184 mTurk participants completed the questionnaire (in English) and 334 in COPA (in Dutch). Internal reliability was acceptable (mTurk α=0.89; COPA α=0.94). Construct validity was confirmed, with significant correlation between MPRAQ and BMQ-Specific Concerns (mTurk r=0.546, p<0.0001; COPA r=0.370, p<0.0001); BMQ-General Harm (mTurk r=0.504, p<0.0001; COPA r=0.219, p<0.0001); BMQ-General Overuse (mTurk, r=0.324, p<0.0001; COPA r=0.109, p=0.047), and PSM (mTurk only, r=0.463, p<0.0001), and a negative correlation with MARS-5 (mTurk r=-0.450, p<0.0001; COPA r=-0.260, p<0.0001). MPRAQ did not correlate with BMQ-Specific Necessity or BMQ-General Benefit. Correlation between MPRAQ baseline and 2-week follow-up scores confirmed test-retest reliability (r=0.745, p<0.0001; n=52).

Conclusion: MPRAQ is a reliable and valid self-report measure of practical adherence barriers.

Highlights (50 word limit/statement)

What is already known about this subject

- Several questionnaires currently exist that measure medication adherence. However, existing measures focus on evaluating medication-taking itself (i.e. adherence) rather than identifying barriers to adherence; where measures do identify adherence barriers, these assess either perceptual barriers only or a mix of practical and perceptual barriers.
- Differentiating between perceptual and practical adherence barriers is important, as the type of interventions that are likely effective will differ depending on the type of adherence barrier. There is a need to have an adherence measure that focuses only on practical adherence barriers, however no current measure exists that evaluates practical adherence barriers specifically.

What this study adds:

What do we now know as a result of this study that we did not know before?

- This paper presents a novel self-report measure – the Medication Practical barriers to Adherence Questionnaire (MPRAQ) – that aims to assess individual's practical barriers to medication adherence.
- The MPRAQ describes 15 different practical adherence barriers to regular medication-taking that individuals may face that might prevent them from adhering to their medication, such as dosing frequency, obtaining medication supplies, and cost.
- The paper reports on the psychometric properties of the MPRAQ, providing evidence of validity and reliability in two different and culturally diverse populations, representing the general public who take medication.

What take-home message do you want to impart to readers?

- Medication adherence is an important determinant of health outcomes and key for informing healthcare-related decision making, as poor adherence leads to suboptimal outcomes.
- Identifying practical adherence barriers is an essential first step to improving adherence as overcoming practical barriers often only require simple changes in the individual's environment, rather than more complex interventions which may be necessary for addressing perceptual barriers.
- This paper reports on a new questionnaire that can specifically measure practical adherence barriers in an individual.

Introduction

Poor medication adherence remains one of the key barriers to achieving optimal outcomes from treatment, with poor adherence being associated with a higher risk of morbidity and mortality[1]. Improving adherence to treatment is challenging. Many factors influence medication adherence, ranging from perceptual barriers such as an individual's concerns about treatment harm and lack of perceived personal need for treatment, to practical barriers such as difficulties accessing medication and affordability of the treatment[2-4]. There is a significant overlap between perceptual and practical factors influencing adherence[3]. As the reasons for medication non-adherence can vary widely between and within an individual over time, there is a need for methods to efficiently and accurately identify an individual's unique adherence barriers. This is reflected in the current UK National Institute for Health and Care Excellence (NICE) guidelines on medication adherence[5]. The guidelines highlight the importance of identifying in a non-judgemental way the specific factors that influence medication adherence for an individual, so that adherence interventions can be tailored to the individual according to the identified factors. This is also in line with the Perceptions and Practicalities Approach (PAPA) to adherence intervention design, whereby tailored interventions designed to address the perceptions (e.g. beliefs about illness and treatment) and practicalities (e.g. capability and resources) affecting motivation and ability to adhere to treatment are more effective[3, 6]. A key first step of any adherence intervention is therefore being able to accurately identify the factors that influence medication-taking in a systematic and accurate way so that individualised interventions addressing these factors can be designed .

In most healthcare settings, there is a limited amount of time in clinical consultations to explore the adherence barriers facing an individual. A brief, pragmatic questionnaire that can quickly and accurately identify the specific factors that influence medication adherence in an

individual can therefore be useful for better informing clinical management and consultations. Many adherence measures currently exist, yet these focus either on assessing adherence alone, or is a questionnaire that measures both adherence and identifies adherence barriers, rather than focusing on the latter specifically[7]. Questionnaires that do focus on barriers to adherence do not tend to differentiate between perceptual or practical barriers. It is important to differentiate between the two types of adherence barriers, as the type of interventions that are effective for overcoming these barriers are likely to differ between perceptual versus practical barriers, even though there is overlap between the two[3, 4]. Horne et al. describe medication adherence as a behaviour that is influenced by an individual's motivation and ability, with one influencing the other – deficits in ability may be overcome with motivation [3, 8]. Changing one type of barrier can thus impact the other, as illustrated by studies which show the negative influence of complex regimes on motivation to take medication [5, 8]. Being able to precisely measure and change the primary type of adherence barrier facing an individual can influence other barriers and help with refinement and tailoring of interventions. For example, perceptual barriers tend to be the primary driver of intentional non-adherence, where an individual does not adhere to treatment because of their personal judgements, beliefs and motivations towards the treatment, rather than a lack of ability[9]. Practical barriers on the other hand tend to promote unintentional non-adherence, where an individual does not adhere due to a lack of ability to take or access the treatment, rather than their own preferences and beliefs. Different behaviour change interventions are needed depending on the type of adherence barriers facing an individual[5]. Addressing perceptual barriers generally require more complex behaviour change interventions which aim to shift individual perceptions and beliefs, compared to interventions to address practical adherence barriers. Practical barriers are generally overcome by changes in an individual's environment or context, rather than a shift in perceptions or beliefs. At present, there are

measures that assess perceptual barriers such as the Beliefs about Medicines Questionnaire (BMQ)[10], however these do not capture practical barriers to adherence. There are some questionnaires that exist that do assess practical barriers but they do so only in a few items as part of a larger adherence measure, such as the Adherence Estimator[11] and the Living with Medicines Questionnaire[12]. A recent review of adherence measures that assess practical adherence barriers identified 23 unique measures that assess practical barriers, however none of these 23 measures capture all types of practical adherence barriers that exist – for example, the Adherence Estimator and the Living with Medicines Questionnaire only explore 1 and 3 types of practical barriers respectively [13]. No questionnaire currently exists that examines all aspects of practical adherence barriers and focuses specifically on identifying practical barriers to medication adherence in a thorough and systematic fashion.

Aims and objectives

The aim of this study is to develop and validate a new self-report measure that specifically identifies practical barriers to medication adherence.

Specifically, the study objectives are:

- To develop a series of questionnaire items that describe practical barriers to adherence to inform the development of a new self-report measure that specifically identifies practical barriers to medication adherence;
- To evaluate the questionnaire items in a sample of patients taking medication to assess face validity and refine the questionnaire based on feedback;
- To determine the reliability (internal and test-retest), validity (construct and discriminant) and acceptability of the new questionnaire in two diverse samples representing the general public who are on medication

Methods

Development of questionnaire items

The items on the Medication Practical barriers to Adherence Questionnaire (MPRAQ) were developed to assess practical barriers to adherence. Fifteen items were developed based on a review of the literature of practical adherence barriers to treatment[13]. The review identified seven types of practical adherence barriers relating to formulation; instructions for use; issues with remembering; capability – knowledge and skills; financial; medication supply and social environment. These findings from this review was evaluated by the multidisciplinary research team comprising experts from pharmacy, psychology, behavioural science, patient experience, and academia and items developed based on these key themes reported, making sure that items were included that addressed the barriers described in each of the seven categories. The resulting questionnaire items each refer to a category of practical adherence barriers, such as difficulties physically taking the medication (e.g. swallowing a tablet or giving an injection) or barriers relating to complex administration requirements (e.g. having to take a medication at a particular time of day or having to take medicines at different times), or to medication supply (e.g. knowing where to obtain further supply when medication runs out). Items were worded as statements reflecting practical adherence barriers that previous studies in adult patients taking regular prescribed medication without assistance have been reported in the literature[13-18] (e.g. The number of times I have to take my medication every day is difficult for me). The decision to word the questionnaire items in a statement format was to support respondent self-completion of the questionnaire, with the items written in a way that could be easily understood by the majority of the respondents, and to present the barriers in a non-judgemental way to normalise the barriers, reduce reporting bias and promote truthful responses[19]. Participants were asked to score their level of agreement with each questionnaire item using a 5-point Likert scale, with higher scores indicating stronger

agreement with the statement. This means that participants scoring highly on the MPRAQ have more practical barriers to adherence. The use of a Likert scale was chosen over a binary yes/no scale to improve the quality of the information obtained[5, 20].

An introductory statement to the questionnaire was added to inform participants how the MPRAQ should be completed and to normalise adherence barriers in a non-judgemental way to reassure respondents they could provide honest responses without being judged[5, 20, 21]. There was discussion about how the MPRAQ should be used for individuals who are taking more than one medication. Whilst adherence barriers can be different for different medications[22], the MPRAQ is intended to provide clinicians and /or researchers an overall holistic assessment of the practical adherence barriers an individual faces. As such, and in line with other similar self-report questionnaires[20, 21], the MPRAQ instructions asks respondents to provide their overall feeling about all their medicines if they are using more than one medicine.

Face validity and questionnaire refinement

Initial face validity was evaluated in patients with Type-1 (T1D) and Type-2 (T2D) diabetes recruited from a local patient support group for diabetes in Harringay, London. A diabetes group was initially chosen for face validity testing as individuals with diabetes commonly have other comorbid general medical conditions and represent a range of ages; following this initial refinement, further testing was then conducted in a general population (see later section). Two research assistants facilitated the focus group, who explained that the research was conducted as part of a wider piece of market research in diabetes with the objective of identifying practical barriers to medication-taking. The researchers informed the participants verbally and in written format, that the market research is non-promotional in nature, and abides by all industry guidelines (British Healthcare Business Intelligence Association -

BHBIA). As the research was conducted in accordance with the BHBIA Legal and Ethical Guidelines for Healthcare Market Research, approval from the Research Ethics Committee was not required as it falls outside the remit of the Research Governance Framework[23]. Participants did not receive remuneration for participation. The group facilitators invited the participants to complete the draft questionnaire on their own, individually and without assistance from the facilitators, though the facilitators were on hand to answer any questions from the participants. Participants were informed that the questionnaire describes statements other people have made about difficulties taking medicines, and that they could indicate how much they agreed or disagreed with the statement by ticking the appropriate box. Participants were informed that there were no right or wrong answers, the team were simply interested in their personal views. Participants were also asked to complete some basic demographic questions relating to their age, sex, diabetes diagnosis (Type 1 or Type 2); and duration of diagnosis (in years). Following questionnaire completion, the research assistants invited participants to give written and verbal feedback on any difficulties they faced with completion of the questionnaire. Specifically, the participants were asked to complete the following questions on the written questionnaire form: "Is there anything else that stops you from taking your medication as prescribed (that is not captured by the questionnaire)?(free text); Did you find the wording of the questions easy to understand? (Yes, No, Unsure); How did you find the length of the questionnaire? (Good length, Too short, Too long); How long did it take you to answer it? (minutes); Are there any questions you didn't understand? If so, please state which number question(s) you didn't understand (free text); Did you find any of the questions repetitive? If so, please state which number question(s) (free text); Is there any other feedback you would like to give about the questionnaire?(free text). The group facilitators then followed up with verbal discussion to invite any further feedback and

comments on the questionnaire. Field notes were taken for the verbal feedback and data analysed descriptively to inform questionnaire refinement.

Reliability, validity and acceptability testing

Further reliability and validity testing of the questionnaire was then completed in two samples from general populations: an Amazon mechanical Turk (mTurk) sample, and a consumer panel from the Netherlands (COPA) sample (see Figure 1 for an overview of study processes). These two populations were chosen for psychometric testing to allow evaluation of the MPRAQ in two culturally diverse populations with differing methods of recruitment (online sample versus a consumer panel sample), as described below. Both samples had to have experience of self-managing/taking medication as the populations represented members of the public who were prescribed medication.

Participant recruitment – mTurk sample

Participants were recruited using the Amazon Mechanical Turk (MTurk) platform, an online participant recruitment portal in which participants are reimbursed with small monetary rewards[24, 25]. The sample is predominantly English-speaking and a filter was chosen to select only for mTurk participants based in the United Kingdom (UK) (see below *study procedures*). MTurk has been used in health research across different health conditions[24, 26] due to its ease to recruit large diverse samples rapidly, and cost-effectiveness, with characteristics and demographics that seem to be largely comparable to traditional research samples.[24, 26] The mTurk sample completed the questionnaire in English only.

Participant recruitment – Dutch consumer panel (COPA)

For the second participant sample, participants were accessed through the Dutch Health Care Consumer Panel (COPA) of Nivel (Netherlands institute for health services research). This panel aims to measure the attitudes, expectations and experiences towards, and knowledge of,

health care among a cross section of the Dutch population. For more information about the panel see Brabers et al., 2015[27]. COPA is an access panel and consists of a large number of Dutch-speaking people who have agreed to answer questions on a regular basis. There is no possibility for people to sign up for the panel on their own initiative, to ensure the panel represents a wide range of individuals. The panel is refreshed on a regular basis to ensure that members do not develop specific knowledge of, or interest in, certain healthcare issues, and that no questionnaire fatigue occurs. Participants can indicate a preference to be approached with either a postal or an online questionnaire. Several socio-demographic and health information details of the participants are known, such as age, gender and highest level of education and health conditions. At the time of the study (November 2018), the access panel consisted of approximately 12,000 people aged 18 years and older. Each individual panel member receives a questionnaire approximately three to four times a year and can quit the panel at any time. New members of the panel are sampled from the general population.

The COPA sample completed the questionnaire in Dutch. The questionnaire was translated by one of the authors (LvD), with the translation reviewed by two other researchers and the advisory board of COPA.

Study procedures – mTurk platform

The online survey that participants completed in this study was created using the survey platform Qualtrics (http://www.qualtrics.com) and then hosted on the mTurk platform. Participants self-selected by responding to the survey if they met the inclusion criteria: aged at least 18 years old, and currently taking and self-managing their own medicines. This was identified using screening questionnaires at the beginning of the survey; those who confirmed they met the inclusion criteria were eligible to participate. As the survey contained a

significant amount of text, participants were recruited from the UK only in order to maximise the number of respondents proficient in reading English.

Participants completed the MPRAQ, and questions relating to their perceptions of the questionnaire (specifically, whether there were any questions they did not understand (and which), whether they found any of them repetitive (and which), and if they had any other feedback pertaining to the questionnaire). Following this, participants completed a range of other questionnaires to assess construct validity (see construct validity section). These questions included: the BMQ[10], 5-item Medication Adherence Report Scale (MARS-5)[21], and the Perceived Sensitivity to Medicines Questionnaire (PSM)[28]. The BMQ is a widely-used validated questionnaire to assess an individual's perceived personal need for treatment and concerns about medicines. There are two parts to the questionnaire – one relating to specific medicines (BMQ – Specific) and one relating to general beliefs about medicines as a class (BMQ – General) – participants were invited to complete for the specific and general BMQ. The MARS-5 evaluates medication adherence, and the PSM measures an individual's beliefs about their personal sensitivity to the negative effects of medicines e.g. side effects or medication reactions (see construct validity section for more detail).

Once all questionnaires had been completed, participants were asked to give a unique identifier, created using the last two digits of the year they were born (e.g. 81); the first two letters of their mother's first name (e.g. BA); and the first two letters of the town they were born in (e.g. LO). This unique identifier was created to match up each participants' responses at baseline with their follow-up responses. As part of reliability evaluation, participants were invited two weeks after completion of the first survey to complete the MPRAQ a second time.

Participants received a payment of US$1 for completion of the first survey, and US$1 for completion of the two-week follow-up. Participants were invited to complete only one questionnaire – the MPRAQ – at follow-up; despite the shorter time required for survey completion, the same follow-up payment rate was offered to increase the incentive for participants to complete the follow-up.

According to an online review by the UK NHS Research Ethics Committee, and the University College London ethics policies, no further ethical approval was deemed necessary for this study, as the mTurk survey did not collect any identifying data, and involved the use of non-sensitive, completely anonymous survey procedures [29, 30].

Study procedures – COPA

The questions used for this study were part of a larger questionnaire which also included questions on general practice care and on trust in medication. Participants completed all questionnaires in Dutch, as all members of the panel are native Dutch speakers, or speak Dutch at a level that they can fill out questionnaires in Dutch. Participants were invited to complete the MPRAQ, the BMQ (both the specific and general)[10], and the 5-item Medication Adherence Report Scale (MARS-5)[21]. The questionnaire was sent online in November 2018 to a sample of 1,500 members representative of the general population in the Netherlands aged 18 years and older in terms of sex and age. Three electronic reminders (after one and after two and after almost three weeks) were sent to panel members who had not yet responded. The closing date for sending in the questionnaire was three and a half weeks after the initial sending. The questions used in this study were only posed to those participants who used prescription medicines at least once in the last 12 months. Data were analysed anonymously, and processed according to the privacy policy of the Dutch Health Care Consumer Panel, which complies with the General Data Protection Regulation (GDPR).

According to Dutch legislation, there is no legal requirement to obtain informed consent, nor approval by a medical ethics committee for conducting research through the panel[31]. Moreover, informed consent to be part of the panel is obtained from COPA participants, who fill in about 4 questionnaires a year[32].

For both samples, prior to data analyses, data checks were conducted to ensure participants were completing the questionnaires approriately (e.g. participants who provided the same response to every question were excluded).

Analyses

Univariate analyses

Descriptive analyses of each questionnaire item were conducted to describe the means, standard deviations and frequency distributions of participants' responses to each of the items. This item analysis identified the percentage of respondents who responded agree/strongly agree to each of the scale items.

Reliability analyses

An internal reliability analysis assesses the consistency of results across items within a questionnaire, and is useful for determining the value that each respective scale item adds to the overall questionnaire. This analysis was used as it was assumed that the items in the MPRAQ are related, based on the relationship between practical barriers and adherence[8]. This analysis produces Cronbach-alpha values for each scale item, and for the questionnaire as a whole. Cronbach-alpha values are the widely accepted measure of internal reliability (Cronbach-alpha >0.7 acceptable) and indicate how closely related a set of scale items are as a group[33]. This enables researchers to determine how necessary it is to include each specific item within the questionnaire.

Cronbach's alpha value was calculated for each questionnaire item, to assess each items' contribution to the scale and whether the alpha value would improve if the item was deleted. Cronbach's alpha was also calculated overall with all the items combined in MPRAQ to assess the questionnaire's internal reliability as a whole.

Test-retest reliability determines the stability of a test over time, and considers the likelihood that a given measure will give the same results if repeated in the same participants. To assess test-retest reliability, Pearson's correlation coefficients were calculated for MPRAQ composite scores collected at baseline, and at two weeks' follow-up in the mTurk sample. This was not done in the COPA sample as the data collection in the panel only occurs as a one-off cross-sectional survey.

Validity testing

Construct validity

Construct validity assesses the extent to which a questionnaire actually measures what it intends to measure, for example that the scores do predict the theoretical trait it says it does. Construct As no 'gold standard' exists in terms of determining existence of practical adherence barriers, we judged construct validity based on how the composite scores on MPRAQ related to validated measures of beliefs about medicines, medication adherence, and perceived sensitivity to medicines, using Pearson's correlation coefficients.

Table 1 describes the hypotheses which were used to determine construct validity. These measures are described in detail below:

1. Beliefs about medicines (BMQ) (specific)

The BMQ – Specific questionnaire consists of two subscales – the Necessity and Concerns subscales. As practical adherence barriers represent difficulties with their ability to take the treatment, we hypothesise that patients with fewer practical adherence barriers would report

greater motivation to take treatment (i.e. higher necessity, and lower concerns) (as less complex regimens for example would support lead to higher motivation to take the treatment)[8]. This means that participants who score lowly on the MPRAQ (i.e. have few practical adherence barriers) would have higher necessity beliefs and lower concerns, about their medication.

2. Beliefs about Medicines (General)

The 12-item BMQ-General was used in this study to evaluate general beliefs about medicines. This consists of three subscales – one related to beliefs that medicines are overused (BMQ General-Overuse), another describing beliefs that medicines are harmful (BMQ General – Harm), and one describing benefits of medicines (BMQ General – Benefits). Similarly to our hypothesis about the relationship between practical barriers and necessity and concerns, we hypothesised that participants with more practical adherence barriers (higher MPRAQ) would have stronger beliefs about medicines overuse and harm (higher scores on the Overuse and Harm subscales), and weaker beliefs about medicines benefits (lower scores on the Benefits subscales).

3. Medication adherence

Medication adherence was assessed using the MARS-5. The questionnaire consists of 5 statements, each describing a behaviour related to non-adherence. Participants rate how often they behave as describe by the statement e.g. '*I alter the dose'* using a 5-point scale (Always = 1, Never = 5), with higher scores indicating better adherence. As practical adherence barriers represent difficulties with taking treatment, we predict that participants scoring highly on the MPRAQ (i.e. more practical difficulties with taking treatment) would have lower scores on the MARS (i.e. poorer adherence).

4. Perceived Sensitivity to Medicines (PSM)

Individuals may vary in the perception of personal sensitivity to negative effects of medicines. The PSM is a 5-item questionnaire that comprises statements that describe beliefs about personal sensitivity to medicines e.g. *'My body is very sensitive to medicines'*. This questionnaire was administered only in the mTurk sample, with the hypothesis that individuals who believe they are highly sensitive to medicines are more likely to experience difficulties with medication-taking. As such, we expected a positive relationship between the two parameters with those scoring highly on the MPRAQ having higher scores on the PSM.

Discriminant validity

Discriminant validity determines whether or not data that are intended not to be related, are in fact unrelated and independent. An independent-samples t-test was used to determine the discriminant validity of the MPRAQ and explore if there was a significant difference in MPRAQ total scores between those reporting low adherence versus high adherence on the MARS. The cut-off score for the low and high adherence scores was based on the scoring of the 5-item MARS – a score of 20 or above indicates at least agreement with all items (i.e. a Likert score of 4 for all 5 items), thus indicating high adherence versus those scoring 19 or below. To check whether a different cut-off score would impact the validity findings, a sensitivity analysis was conducted using a cut-off score of 15. As current literature shows there is no gold standard for dichotomising the MARS[34], and different opinions exist to what the cut-off should be[35], a cut-off was chosen to represent the 'middle' score of '3' on the 5-point Likert scale in the 5-item questionnaire (3 x 5 items = 15).

Acceptability

Questionnaire acceptability was also further evaluated in the mTurk sample. This was assessed on three acceptability domains: whether or not they found the questionnaire easy to understand (yes/no); whether or not they found the questionnaire repetitive (yes/no), and

what they thought of the questionnaire length (too long / too short / good length). Where respondents rated 'no' to either of the first two questions, or responded 'too long' or 'too short' for questionnaire length, respondents were asked to identify which statements were problematic. Open-ended feedback was also invited via a free-text comments box at the end of the questionnaire.

Results

Face validity

A total of 15 people (5 T1D; 10 T2D) completed MPRAQ (46% female; mean ±SD age 64 ±12 years (range 34-86 years); mean length of diagnosis 41 ±25 years for T1D (range 15-65 years) and 17 ±5 years for T2D (range 8-28 years)). The questionnaire was well accepted by patients, with 93% (14/15) respondents indicating that the questionnaire was a "good length", and none of the questions were repetitive. Overall participants took a self-reported mean(SD) of 4(2) minutes (range 2 to 10 minutes) to complete the questionnaire. All respondents indicated that the wording of the questions were "easy to understand" and that the questionnaire captured their practical difficulties with medication-taking accurately, confirming face validity. All but one respondent stated they understood all the question statements – the one respondent who fed back on issues with the questionnaire wanted clarification on whether the question related to just one or all of their medication. Feedback from participants led to changes in wording of some questionnaire items, for example changes in the language for clarity and rewording of some items so the focus was on the medication not the individual (see Appendix 1). These changes were incorporated into the MPRAQ prior to the testing in the mTurk and COPA samples.

Participants – mTurk sample

A total of 184 participants completed the first survey, and 52 participants completed the two-week follow-up. Participants took a mean (SD) time of 541 (604) seconds to complete the survey. Of the 184 participants, 163 stated their age – the mean (SD) self-reported age of the sample was 31.1 (8.3) (range = 18-67 years). 14/184 stated they had other difficulties preventing them from taking their medicines – these related to concepts already captured by the MPRAQ such as difficulties with swallowing (n=2), taste (n=1) or remembering to take medication (n=1), or were not related to practical barriers such as side effects (n=2), or lack of motivation or perceived need to take medication (n=2). The additional barriers fed back by participants that were not captured by the MPRAQ were about the smell of the medication (n=1), social circumstances (e.g. finding somewhere quiet and clean to inject medication) (n=1), not having a supply on hand at the time the dose is due (n=3).

Participants – COPA sample

The overall response to the questionnaire was 50.2% (n=753 respondents). Mean (SD) age of respondents was 60.8 (12.8) years, ranging from 30 to 89 years. Of these respondents, 334 participants used prescription medicines at least once in the last 12 months and were included in the final sample for analysis. The demographics of the final included COPA respondents are in Table 2.

MPRAQ univariate analysis

Table 3 shows the means, standard deviations of each of the participants' scores to the MPRAQ and the percentage of respondents rating agree/strongly agree to each statement in both the mTurk and COPA samples. Higher scores indicate greater practical adherence barriers. This shows that overall the COPA sample reported fewer practical barriers to

treatment, with a lower overall mean score and less response variability than the mTurk sample.

MPRAQ internal reliability

The analysis of the 15-item practicalities questionnaire highlighted that all scale items held equal value to the questionnaire (as indicated by similar Cronbach-alpha values for each scale item) (Table 4). The questionnaire showed good internal reliability , with alpha = 0.89 in the mTurk sample and alpha = 0.94 in the COPA sample for the overall scale.

Construct validity

1. BMQ Specific

As expected from the study hypothesis, there was a strong positive correlation between MPRAQ scores and concerns (mTurk: r=0.546 p<0.0001; COPA: r=0.370, P=<0.0001), indicating that participants with greater practical barriers to adherence had higher concerns about treatment. This aligns with the study hypothesis. Unexpectedly, a positive but weaker correlation was observed between necessity beliefs and MPRAQ scores (r=0.205, p=0.005) in the mTurk sample; this was not found in the COPA sample where there was no relationship between necessity scores and MPRAQ (r =0.18, p=0.748).

2. BMQ General

As predicted from our study hypotheses, there was a positive correlation between the BMQ Overuse (mTurk: r=0.324, p<0.0001; COPA: r=0.109, p=0.047) and Harms subscales (mTurK: r=0.504, p<0.0001; COPA: r=0.219, p<0.0001) and the MPRAQ, indicating that individuals who have high concerns about medication overuse and harms also reported greater practical barriers to adherence. For the BMQ Benefits subscale, which was only

administered in the mTurk sample, there was no significant relationship seen between the BMQ Benefits scores and the MPRAQ (r=-0.119, p=0.108).

3. Medication adherence

A significant negative relationship was seen between the MARS and MPRAQ scores in both samples (mTurk: r=-0.450, p<0.0001; COPA: r=-0.260, p<0.0001) indicating that respondents with greater practical barriers to adherence self-reported poorer adherence, confirming the study hypothesis.

4. Perceived Sensitivity to Medicines (PSM) – mTurk only

Respondent scores on the PSM were significantly positively correlated with MPRAQ scores in the mTurk sample (r=0.463, p<0.0001), confirming the study hypothesis that individuals with a high perceived sensitivity to medicines also reported facing more practical barriers to medication-taking.

Discriminant validity

The MPRAQ showed good discriminant validity with a clear differentiation between participants with high vs. low adherence scores on the MARS (mTurk: $f = 0.743$, $t = -4.285$, $p < 0.0001$; COPA: ($f = 0.027$, $t = -2.949$, $p = 0.003$). As predicted, respondents with low self-reported adherence had significantly higher scores on the MPRAQ indicating greater perceived practical barriers to treatment (mTurk: mean ±SD) MPRAQ in the low vs. high adherence group = 38.9 ±11.4 (n=87) vs. 31.9 ±10.5 (n=97); COPA: mean ±SD MPRAQ in the low vs. high adherence group = 28.2 ±9.4 (n=43) vs. 24.0 ±8.4 (n=291)). The means difference in MPRAQ between high vs. low adherence respondents was in the mTurk sample = 6.9 (95% CI, 3.7 – 10.1) and COPA sample = 4.1 (95% CI, 1.4 – 6.9). The sensitivity analysis using a cut-off score of 15 on the MARS to differentiate between high vs. low adherence participants did not change the observed findings in the mTurk sample ($f = 2.265$, t

= -4.863, $p < 0.0001$); for the COPA sample, the sensitivity analysis could not be conducted, as only 1 participant scored <15 on the MARS.

Test-retest reliability – mTurk sample only

Overall MPRAQ score at baseline for the 52 mTurk participants who completed both timepoints was 32.9 (9.6) versus 33.4 (10.5) at two weeks. Participants took a mean (SD) time of 517 (254) seconds to complete the follow-up. Of the 52 follow-up participants, 50 reported their age, giving a mean (SD) age of 32.6 (8.6) years, which is similar to the baseline age for the full baseline sample of 184 participants. There was a strong correlation between the two timepoints (r=0.745, p<0.0001). The correlations were significant for all 15 items individually on test-retest, though items 3 and 6 had the lowest correlation and significance (item 3 r=0.347, p=0.012); (item 6 r=0.374, 0=0.006).

Acceptability – mTurk sample only

Most mTurk respondents (97%, 179/184) rated the questionnaire as easy to understand – of the 5 participants who stated they had difficulties with understanding some of the questions, there was no consistency in the question number which posed issues. A third of participants (31%, 57/184) felt the statements were repetitive particularly questions 1, 9, 13, 14 and 15. Most felt the questionnaire was of a good length (92%, 169/184), though interestingly 6% (11/184) felt it was too short, and 2% (4/184) too long. Thirteen participants gave further feedback on the questionnaire – these were generally positive with many feeding back that the questionnaire was interesting and useful, and had 'good content'. Three participants felt that the questionnaire would be more helpful if it focused on a specific medication.

Discussion

This study reports on the development of a new self-report measure of practical adherence barriers to treatment. The study confirmed the reliability (internal and test-retest) and validity

(face, construct and discriminant validity) of the new MPRAQ scale. Barriers to adherence can often be difficult to elicit from patients in consultations which are limited by time and resource. Furthermore, patients may find it difficult to share the practical issues they are facing with medication-taking due to fears of being judged, or concerns about impact on access to medication and care.

The MPRAQ can serve as an important starting point to begin conversations with patients about their medication taking and the adherence barriers they face in a non-judgemental way. The wording used in the questionnaire items was deliberately used to describe common practical problems that patients face with medication-taking to normalise the issues. This study provides robust pilot data to support the potential use of this questionnaire to identify practical barriers to treatment that may be amenable to intervention. The current instructions of the MPRAQ reflects this, as it asks respondents to consider their overall feeling about all their medicines if they are using more than one medicine. This approach was chosen as the MPRAQ is intended to be used to initiate adherence discussions with the patient, and this holistic approach serves to provide health providers an idea of where the individual sits on the spectrum of practical adherence barriers. However, adherence barriers are likely to be different depending on the specific medication[22]. There is potential the MPRAQ can be used for specific medication to tailor discussions; how this approach performs in practice needs further evaluation. The MPRAQ also showed good discriminant validity for patients with high versus low adherence scores. Further evaluation of discriminant validity using more objective measures of adherence, such as prescription refill data, would be useful to confirm these findings. There is potential for the questionnaire to be used with other measures such as the BMQ or with measure of disease control (e.g. blood pressure, laboratory parameters) to develop an overall picture of the individual's adherence and response to treatment, to inform better clinical decision-making.

Strengths and limitations

One key strength of this questionnaire is the method through which the MPRAQ was developed. To determine face validity and acceptability of the questionnaire, we initially tested the questionnaire with a sample of patients on long-term medication; from our experiences, it would be prudent to ensure face validity is checked with the target end user population (i.e. individuals taking long-term medication) to ensure that items are interpreted the way they are intended[36]. We identified several changes through patient feedback which were implemented into later versions of the questionnaire. A limitation of our face validity testing was that it was conducted with a small sample of patients from the same diabetes support group, all with the same chronic condition and only in English. Individuals who attend support groups may be more motivated and engaged with their health, and thus may not represent the general public on medication. Testing would have been strengthened if this had been evaluated in a more diverse population, outside of the patient support group and in other health conditions, and in both English and Dutch, to support the later validation in a Dutch-speaking population. Additionally, we did not collect data on other factors that may have influenced medication-taking in this group (e.g. employment), which may have better informed the face validity testing.

Another strength of our study is the use of two different samples recruited by different means and representing two culturally diverse populations to evaluate the reliability and validity of the MPRAQ. This led to an overall large sample size for testing. Current guidelines recommend having 10 respondents per item for questionnaire testing[37] though others have suggested that a graded scale of sample sizes be used for scale development, with 100 = poor and ≥ 1000 = excellent[38]. In our study we had a total of 518 respondents which equates to a nearly 35 respondents per item, or a rating of "very good" in terms of sample size for scale development[37, 38]. We found similar results across both samples which confirm the

reliability and validity of this questionnaire across different populations recruited from different countries, and in two different languages (in English and in Dutch). Unfortunately due to resource limitations, we were not able to perform a backward translation of the questionnaire in Dutch to ensure accuracy of the translation, in line with recommendations for questionnaire translation; however, we followed the recommendations for other aspects – i.e. involving at least two independent translators during the forward translation process, and consulting with an expert committee to review the translated questionnaire[19]. Further testing of the Dutch version in other populations may be needed.

We were also not able to collect demographic data from our mTurk sample to confirm which populations our findings might be generalisable to. Although we found good test-retest reliability, we were not able to check that the participants were taking the same medication in both time periods to confirm the reliability of the test-retest, though it is unlikely that participants would have had medication changes in the 2-week follow-up timeframe. Furthermore, only 52 of the original 184 participants (28%) completed the follow-up. Although the follow-up sample were similar in age to the full baseline sample, no additional data on other characteristics were available to draw comparisons between responders and non-responders to the follow-up. Future testing of test-retest reliability in other populations is needed. Samples were self-selected individuals in the mTurk sample – how the questionnaire performs in a real-world clinical sample of patients with different diseases needs to be determined. However, current evidence from the COPA dataset (which are not self-selected individuals) are in line with our mTurk findings, which confirms in part MPRAQ validity and reliability in these populations. Additionally, previous literature suggests the response from these panels do reflect responses from populations recruited via traditional research means[26], though further testing is needed to confirm this. Nearly a third of the respondents

from the mTurk sample felt there was repetition within the MPRAQ items. Additional testing in larger populations to identify areas for refinement is warranted.

Interestingly, differences in construct validity were observed between the mTurk versus COPA samples. Overall, the mTurk sample reported more practical barriers, and showed stronger relationships for the construct and discriminant validity tests. The differences between the two samples may potentially reflect the more general nature of the COPA sample, as it the COPA sample is intended to represent the general population, or the mTurk sample may comprise more unwell patients, since the COPA sample reported fewer practical barriers and also fewer concerns in general, including fewer concerns about medicines overuse and harm, and better adherence than the mTurk sample (data not shown). The differences in inclusion criteria may explain some of this, as the mTurk sample needed to be self-managing their own medicines to be included and were generally younger, whilst the COPA sample was older and there was no inclusion criterium relating to medication self-management. Some participants may therefore have reported fewer practical barriers if they were receiving support for their medication management. The COPA sample also completed the MPRAQ as part of a larger study on general practice care and trust in medication. The older age of the COPA sample and the influence of the larger study may have influenced respondents to report fewer practical barriers as personal experiences of healthcare and /or of medication-taking can affect adherence[39], though the evidence on the effects of age and disease duration are not consistent[40]. The lack of available demographic information for the full mTurk sample limits our ability to explain the differences observed.

It is possible that the inclusion criterium of having 'used prescription medicines at least once in the last 12 months' in the COPA sample may have contributed to these findings as some respondents may have only taken a short-term course of medication e.g. analgesia or antibiotics and thus did not report many practical adherence barriers. The demographics of

the sample though suggest that this may only relate to a small percentage of the population (only 33 responses selected for 'no chronic illness'); future studies evaluating how MPRAQ behaves for individuals on long-term versus short-term medication are needed as practical barriers are likely to be different between individuals on long-term versus short-term medication.

How our findings about practical barriers relate to beliefs about medicines need further exploration. The literature shows that there is a relationship between ability and motivation, where changes in ability (e.g. changes to medication regimes to reduce complexity) can positively influence motivation to adhere. In the model of adherence posited by Jackson et al., capability influences motivation which affects adherence[8]. This has been reported by Nunes et al. where individuals with complex regimens choose to take medications that offer symptom relief, or medications that are for their most feared condition[5]. This illustrates how ability can influence treatment necessity. Whilst a relationship was seen between MPRAQ scores and BMQ-concerns, no consistent relationship was seen between MPRAQ scores and the BMQ-necessity and BMQ-Benefits subscales. Potentially this suggests that practical adherence barriers may not be related to beliefs about necessity and medication benefits, and that practical barriers may not influence perceptions about treatment necessity or medication benefits. This observation will need further evaluation to understand the relationship between practical barriers and beliefs about treatment, and the direction of the association. Additionally, this study was cross-sectional in nature thus how the MPRAQ behaves over time remains unknown. It was reassuring to see that the MPRAQ had good test-retest reliability but further research on how the scores change over longer periods of time is now warranted.

Conclusion

The MPRAQ is a new self-report measure of practical adherence barriers that demonstrated good internal and test-retest reliability, and good construct validity with a wide range of measures. The questionnaire also showed good discriminant validity with self-reported medication adherence, highlighting the potential utility of this questionnaire as a screener to identify patients at risk of non-adherence. Specifically, the MPRAQ comprises items that are worded to reflect common practical barriers to adherence experienced by individuals, which have been checked by patients for face validity and acceptability of the wording and questionnaire length. Together these findings suggest many potential uses of this questionnaire in research and practice, and represents an important first step towards informing the development of tailored interventions to improve adherence at an individual level.

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Conflicts of interest

AC reports consultancy fees from Janssen-Cilag outside the submitted work. RH reports fees from Medical Innovation Academic Consortium (CASMI), AbbVie, Amgen, Biogen, Idec,

Gilead Sciences, GlaxoSmithKline, Janssen, Pfizer, Roche, Shire Pharmaceuticals, MSD, Astellas, AstraZeneca, DRSU, Novartis, Universitatsklinikum Hamburg-Eppendorf, and Teva Pharmaceuticals, and is the Founder and Director of Spoonful of Sugar Ltd., outside the submitted work.

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Data availability statement

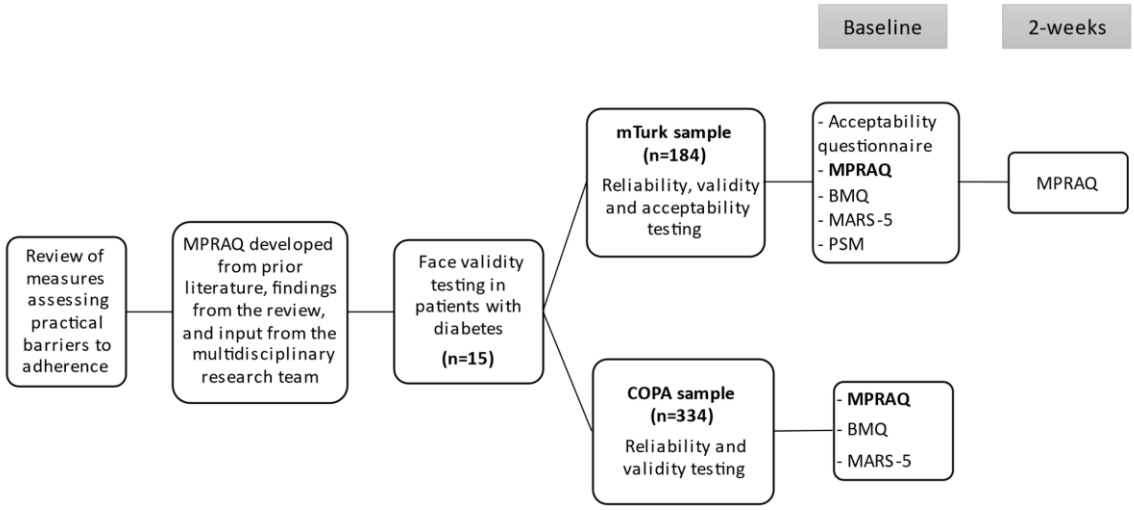
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ (Clinical research ed). 2006; 333: 15.
2. Chapman S, Horne R, Eade R, et al. Applying a perceptions and practicalities approach to understanding nonadherence to antiepileptic drugs. Epilepsia. 2015; 56: 1398-407.
3. Horne R, Cooper V, Wileman V, et al. Supporting adherence to medicines for long-term conditions: a Perceptions and Practicalities Approach based on an extended Common Sense Model. European Psychologist. 2019; 24: 82-96.
4. Linn AJ, van Weert JC, Schouten BC, et al. Words that make pills easier to swallow: a communication typology to address practical and perceptual barriers to medication intake behavior. Patient Prefer Adherence. 2012; 6: 871-85.
5. Nunes V, Neilson J, O'Flynn N, et al. Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Institute for Health and Clinical Excellence, 2009.
6. Kassavou A, Sutton S. Automated telecommunication interventions to promote adherence to cardio-metabolic medications: meta-analysis of effectiveness and meta-regression of behaviour change techniques. Health Psychology Review. 2017: 1-18.
7. Nguyen T-M-U, Caze AL, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. Br J Clin Pharmacol. 2014; 77: 427-45.
8. Jackson C, Eliasson L, Barber N, et al. Applying COM-B to medication adherence: a suggested framework for research and interventions. European Health Psychologist. 2014; 16: 7-17.
9. Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: application of the Necessity-Concerns Framework. Journal of psychosomatic research. 2008; 64: 41-6.
10. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health. 1999; 14: 1-24.
11. McHorney CA. The Adherence Estimator: a brief, proximal screener for patient propensity to adhere to prescription medications for chronic disease. Current medical research and opinion. 2009; 25: 215-38.
12. Krska J, Katusiime B, Corlett SA. Validation of an instrument to measure patients' experiences of medicine use: the Living with Medicines Questionnaire. Patient preference and adherence. 2017; 11: 671-79.
13. Chan AHY, Cooper V, Lycett H, et al. Practical Barriers to Medication Adherence: What Do Current Self-or Observer-Reported Instruments Assess? Frontiers in Pharmacology. 2020; 11: 572.
14. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Frontiers in Pharmacology. 2013; 4.
15. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: a review of the literature. J Gen Intern Med. 2007; 22: 864-71.
16. Martin LR, Williams SL, Haskard KB, et al. The challenge of patient adherence. Therapeutics and Clinical Risk Management. 2005; 1: 189-99.
17. Taylor SA, Galbraith SM, Mills RP. Causes Of Non-Compliance With Drug Regimens In Glaucoma Patients: A Qualitative Study. Journal of Ocular Pharmacology and Therapeutics. 2002; 18: 401-09.

18. Shubber Z, Mills EJ, Nachega JB, et al. Patient-Reported Barriers to Adherence to Antiretroviral Therapy: A Systematic Review and Meta-Analysis. PLoS Medicine. 2016; 13: e1002183.
19. Tsang S, Royse CF, Terkawi AS. Guidelines for developing, translating, and validating a questionnaire in perioperative and pain medicine. Saudi J Anaesth. 2017; 11: S80.
20. Khatib R, Patel N, Hall AS. The my experience of taking medicines (MYMEDS) questionnaire for assessing medicines adherence barriers in post-myocardial infarction patients: development and utility. BMC Cardiovasc Disord. 2020; 20: 46-46.
21. Chan AHY, Horne R, Hankins M, et al. The Medication Adherence Report Scale (MARS-5): a measurement tool for eliciting patients' reports of non-adherence. Br J Clin Pharmacol. 2019; (online first).
22. McHorney CA, Gadkari AS. Individual patients hold different beliefs to prescription medications to which they persist vs nonpersist and persist vs nonfulfill. Patient preference and adherence. 2010; 4: 187-95.
23. British Healthcare Business Intelligence Association. BHBIA Legal and Ethical Guidelines for Healthcare Market Research. Hertfordshire, UK: British Healthcare Business Intelligence Association,, 2020.
24. Burnham MJ, Le YK, Piedmont RL. Who is Mturk? Personal characteristics and sample consistency of these online workers. Mental Health, Religion & Culture. 2018; 21: 934-44.
25. Buhrmester M, Kwang T, Gosling SD. Amazon's Mechanical Turk: A New Source of Inexpensive, Yet High-Quality, Data? Perspectives on psychological science : a journal of the Association for Psychological Science. 2011; 6: 3-5.
26. Mortensen K, Hughes TL. Comparing Amazon's Mechanical Turk Platform to Conventional Data Collection Methods in the Health and Medical Research Literature. J Gen Intern Med. 2018; 33: 533-38.
27. Brabers A, Reitsma-van Rooijen M, De Jong J. Consumentenpanel Gezondheidszorg: basisrapport met informatie over het panel Utrecht: NIVEL, 2015.
28. Horne R, Faasse K, Cooper V, et al. The perceived sensitivity to medicines (PSM) scale: an evaluation of validity and reliability. British journal of health psychology. 2013; 18: 18-30.
29. Central Office for Research Ethics Committees (COREC). Governance Arrangements for Research Ethics Committees. 2018.
30. UCL Research Ethics Committee. Ethics Exemptions. London, UK: UCL, 2020.
31. ccmo.nl. Your research: is it subject to the WMO or not? The Hague: CCMO, 2019.
32. NIVEL. About the Dutch Health Care Consumer Panel. Utrecht, The Netherlands: NIVEL,, 2020.
33. George D, Mallery P. SPSS for Windows step by step: A simple guide and reference. 11.0 update, 4th ed. Boston: Allyn & Bacon, 2003.
34. Hüther J, von Wolff A, Stange D, et al. Incomplete medication adherence of chronically ill patients in German primary care. Patient preference and adherence. 2013; 7: 237.
35. Koster ES, Philbert D, Winters NA, et al. Adolescents' inhaled corticosteroid adherence: the importance of treatment perceptions and medication knowledge. Journal of Asthma. 2015; 52: 431-36.
36. Mes MA, Chan AHY, Wileman V, et al. Patient involvement in questionnaire design: tackling response error and burden. Journal of Pharmaceutical Policy and Practice. 2019; 12: 17.

37. Boateng GO, Neilands TB, Frongillo EA, et al. Best Practices for Developing and Validating Scales for Health, Social, and Behavioral Research: A Primer. Frontiers in public health. 2018; 6: 149-49.
38. Comrey AL, Lee HB. A first course in factor analysis. Psychology press, 2013.
39. Fortuna RJ, Nagel AK, Rocco TA, et al. Patient Experience With Care and Its Association With Adherence to Hypertension Medications. Am J Hypertens. 2018; 31: 340-45.
40. Gast A, Mathes T. Medication adherence influencing factors—an (updated) overview of systematic reviews. Systematic Reviews. 2019; 8: 112.



mTurk: Amazon mechanical Turk – online survey platform used to recruit survey respondents

COPA: Nivel Dutch Health Care Consumer Panel

MPRAQ: Medication Practical barriers to Adherence Questionnaire

BMQ: Belies about Medicines Questionnaire (specific and general)

MAR-5: Medication Adherence Report Scale (5-item)

PSM: Perceived Sensitivity to Medicines Questionnaire

Figure 1: Flowchart depicting MPRAQ development and reliability and validity testing process

Table 1: study hypotheses

	Parameter	**Hypothesis**
1	Beliefs about medicines (BMQ) (specific –necessity and concerns subscales)	Lower MPRAQ scores would be related to higher BMQ-necessity scores and lower BMQ-concerns.
2	Beliefs about Medicines (General) (Overuse, Harm and Benefits subscales)	Higher MPRAQ scores related with higher scores on the Overuse and Harm subscales, and lower scores on the Benefits subscales.
3	Medication adherence	Higher MPRAQ scores related with poorer adherence scores.
4	Perceived sensitivity to medicines (PSM)	Higher MPRAQ scores related with higher PSM scores.

Table 2: Demographics of the Nivel Dutch Healthcare Care Consumer Panel (COPA) sample (n=334)

	N (%)
Gender	
Male	176 (52.7)
Female	158 (47.3)
Self reported chronic illness*	
Asthma, Chronic Obstructive Pulmonary Disease	50 (15.0)
Cardiovascular disease	111 (33.2)
Diabetes	47 (14.1)
Rheumatic illness	83 (24.9)
Malignant disorder or cancer	17 (5.1)
Other	130 (38.9)
None	33 (9.9)
Short-term complaint or illness	101 (30.2)
Self-reported medication types*	
Painkillers	75 (22.5)
Antibiotics	31 (9.3)
Contraceptive	17 (5.1)
Lipid-lowering medicine	102 (30.5)
Anti-hypertensive medicine	130 (38.9)
Blood thinner	65 (19.5)
Diuretics	36 (10.8)
Laxative	14 (4.2)
Medicine for gastrointestinal tract complaints	84 (25.1)

Benzodiazepines (sleeping pill or sedatives)	29 (8.7)
Antidepressants	26 (7.8)
Medicine for other nervous system complaints	9 (2.7)
Antidiabetic medicine	39 (11.7)
Medicine for rheumatic illness	39 (11.7)
Antihistamines	32 (9.6)
Medicine for asthma/Chronic Obstructive Pulmonary	48 (14.4)
Disease	6 (1.8)
Oncolytics	32 (9.6)
Medicine for the skin	31 (9.3)
Medicine for the eyes	89 (26.6)
Other medicine	
Education level[$]	
No/low (primary or pre-vocational education)	39 (11.7)
Moderate (vocational or selective secondary education)	162 (48.5)
High (education provided by universities of applied sciences and research universities)	127 (38.0)

Note:

**Numbers may add to more than 334 as respondents were allowed to select more than one answer this question.*

[$]Where total numbers equate to less than 334, this is due to missing responses for that question.

Table 3: Means, standard deviations and percentage rating agree/strongly agree for each of the MPRAQ scale items in the mTurk and COPA samples

	mTurk sample			**COPA sample**		
Item	**%Agree/Strongly agree**	**Mean**	**Standard deviation**	**%Agree/Strongly agree**	**Mean**	**Standard deviation**
This medicine is very difficult to **take** (e.g. swallow / inhale / inject etc)	29.8	2.41	1.25	5.4%	1.77	0.91
The **number of times** I have to take this medication every day is difficult for me	25.0	2.37	1.17	3.3%	1.69	0.78
The total **number of medicines** I need to take every day sometimes stops me from taking them as prescribed	24.5	2.34	1.26	4.2%	1.63	0.82
It is difficult to **remember** to take this medication	42.9	2.97	1.19	7.2%	1.81	0.91

I am sometimes **too busy** to take this medication	44.6	2.95	1.25	6.0%	1.76	0.88
The **instructions** for this medication make it very difficult for me to use it as prescribed (e.g. taking with food, or at a specific time)	27.7	2.49	1.22	3.9%	1.66	0.79
The extra **monitoring and tests** linked to this medication (e.g. blood tests) gets in the way of me using this medication as prescribed	20.1	2.27	1.14	0.9%	1.63	0.74
I am uncertain about **how to use** this medication (including what it is for)	13.0	1.94	1.10	1.2%	1.52	0.69
My medicine is **very difficult** to take	13.6	1.95	1.10	3.9%	1.65	0.82
I find it difficult to get a new **supply** of	32.1	2.61	1.28	2.4%	1.62	0.74

medicines when I run out						
Cost sometimes stops me from taking my medication as prescribed (e.g. insurance, cost of medication)	34.2	2.58	1.37	2.7%	1.56	0.73
I have trouble **opening** my medication containers	12.5	1.85	1.06	8.7%	1.76	0.96
The **taste** of this medication sometimes stops me from taking it	23.4	2.24	1.22	0.9%	1.50	0.63
The **shape** of this medication sometimes stops me from taking them	15.7	1.99	1.13	0.9%	1.49	0.63
The **size** of this medication sometimes stops me from taking them	21.2	2.24	1.25	1.8%	1.52	0.69
MPRAQ Total		35.21	11.43		24.6	8.66

mTurk: Amazon mechanical Turk

COPA: Nivel Dutch Healthcare Care Consumer Panel

Table 4: Cronbach's alpha of scale if item deleted

Scale item	alpha if item deleted (mTurk)	alpha if item deleted (COPA)
This medicine is very difficult to **take** (e.g. swallow / inhale / inject etc)	0.884	0.937
The **number of times** I have to take this medication every day is difficult for me	0.883	0.934
The total **number of medicines** I need to take every day sometimes stops me from taking them as prescribed	0.883	0.933
It is difficult to **remember** to take this medication	0.897	0.935
I am sometimes **too busy** to take this medication	0.895	0.937
The **instructions** for this medication make it very difficult for me to use it as prescribed (e.g. taking with food, or at a specific time)	0.888	0.933
The extra **monitoring and tests** linked to this medication (e.g. blood tests) gets in the way of me using this medication as prescribed	0.886	0.934
I am uncertain about **how to use** this medication (including what it is for)	0.885	0.935
My medicine is **very difficult** to take	0.882	0.933
I find it difficult to get a new **supply** of medicines when I run out	0.894	0.936
Cost sometimes stops me from taking my medication as prescribed (e.g. insurance, cost of medication)	0.896	0.934
I have trouble **opening** my medication containers	0.889	0.938
The **taste** of this medication sometimes stops me from taking it	0.884	0.934

The **shape** of this medication sometimes stops me from taking them	0.882	0.933
The **size** of this medication sometimes stops me from taking them	0.883	0.933

mTurk: Amazon mechanical Turk

COPA: Nivel Dutch Healthcare Care Consumer Panel

Appendix 1

Changes made to the MPRAQ questionnaire after initial testing

Original wording or format	**Feedback**	**Changes made**
Originally the first items in the questionnaire were specifically about taste, shape and size but this was not applicable to all medicine dosage forms (only applicable to some formulations)	Items that are applicable to only some formulations and not others should be last in the questionnaire.	Move these formulation specific questions about taste, shape, size to the end of the questionnaire
Original wording refers to "my medication" or "my medicines"	Wording lacks clarity in terms of what 'my' refers to.	Replace "my" with "this" – i.e. this medication – for all items where relevant.
I find it difficult to swallow my medication	Increased relevance of this item to different dosage forms (not just oral medicines), and the question wording should focus on the medication not the person.	Reworded to focus on the medication (third person): This medicine is very difficult to **take** (e.g. swallow / inhale / inject etc)
I find the **number of times** I have to take my medication every day difficult	Wording confusing, reworded for clarity	The **number of times** I have to take this medication

		every day is difficult for me
I find it difficult to remember to take my medicines	Question wording should focus on the medication not the person to avoid 'blaming' the individual	It is difficult to **remember** to take this medication
My busy schedule stops me from taking my medicines	Wording difficult to understand in a passive tense – uncertainties around what 'schedule' refers to	I am sometimes **too busy** to take this medication
It is difficult to follow the specific medication-taking instructions given by my doctor or pharmacist (e.g. having to take with food, or at a specific time)	Wording focused on the individual's ability (feels like it is 'blaming' the individual). Reword to a 'third party' format in reference to the medication not the person.	The **instructions** for this medication make it very difficult for me to use it as prescribed (e.g. taking with food, or at a specific time)
The medication monitoring requirements (e.g. blood tests) stop me from taking my medication as prescribed	Clarity needed about 'monitoring requirements' – and monitoring should include tests. Feedback on wording that 'using' in this instance is better than 'taking'/	The extra **monitoring and tests** linked to this medication (e.g. blood tests) gets in the way of me using

		this medication as prescribed
I am unclear about my medication (e.g. what it is for, how or what dose or when to take it)	Statement lacked clarity on what 'unclear' means – reworded for clarity that it relates to 'how to use' this medication	I am uncertain about **how to use** this medication (including what it is for)
The **cost** of the medication stops me from taking my medication as prescribed	Added examples to item wording to ensure that this item relates to different health systems (that cost is cost in general, not just about the medication itself)	**Cost** sometimes stops me from taking my medication as prescribed (e.g. insurance, cost of medication)
The [taste, shape, size] of my medication stops me from taking them	Change from 'my medication' to 'this medication'	The [**taste, shape, size]** of this medication sometimes stops me from taking them