Medication adherence in patients with schizophrenia: a means to an end

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Chapter 6

The Inventory of Medication Intake (IMI): Validation of an Instrument for Assessing Adherence to Antipsychotic Medication

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Abstract

Background: It remains difficult to make a valid assessment of medication adherence in patients with schizophrenia. Several objective instruments are available but limited resources often mean that subjective instruments are used. Unfortunately, the validity of most of the available subjective instruments is poor or unknown.

Objective: To validate a new self-report instrument, the Inventory of Medication Intake (IMI). The IMI is a brief interview and relies on self-reporting about the number of missed doses of antipsychotic medication during a three-week period.

Methods: We evaluated the IMI in a sample of 51 patients with schizophrenia using the Medication Event Monitoring System (MEMS) as a reference. The feasibility, sensitivity, specificity, positive and negative likelihood ratios of the IMI were compared with other subjective instruments, namely the Medication Adherence Rating Scale (MARS), the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), the Compliance Rating Scale (CRS) and a 100-point clinician estimate of medication adherence.

Results: IMI scores were significantly related to MEMS adherence rates ($r=0.445$, $p=0.001$) but the IMI overestimates adherence (sensitivity=36.4; specificity=97.5). Patients detected by the IMI as adherent or non-adherent were in most cases labelled correctly (the positive and negative predictive values were 80.0 and 84.8, and the positive likelihood ratio was 14.6). Adherence among the patients in our sample was high, and this may have affected our results.

Conclusions: The IMI is easy to use and it performed better than other self-report measures. It suffers, however, from poor sensitivity, which limits its usefulness as an instrument for identifying non-adhering patients.

Introduction

Full adherence to antipsychotic medication regimens in schizophrenia patients continues to be a problem for approximately 61% of patients at some time (Valenstein et al., 2006). Over the years, many studies have been performed to understand or cope with non-adherence better. Some of these studies have tried to establish risk factors for non-adherence, while others evaluate the effectiveness of adherence interventions. The measurement of adherence is a crucial issue in these studies.

Several researchers have already found that measuring levels of adherence to a medication regimen is not easy (DiMatteao, 2004; Farmer, 1999; Osterberg & Blaschke, 2005; Velligan et al., 2006). To date, a wide variety of methods have been used. They can be broken down into objective and subjective instruments. Objective methods are blood or urine samples, tracers, pharmacy-based measures, electronic pill monitoring or pill counts. Subjective measures are self-reports, clinician reports or significant-other reports.

Although objective methods are often considered to be more reliable and valid than subjective methods, they too suffer from weaknesses. In general, they are more expensive, complicated, and burdensome, and they also suffer from methodological and validity problems. Concentrations in blood or urine samples and biological markers are not valid indicators of adherence because of interindividual differences in metabolism (Farmer, 1999; Velligan et al., 2006; Cochran & Gitlin, 1988; George et al., 2000). Refill rates and prescription records can be affected by the use of old pills. This approach also requires a closed pharmacy system and it is not useful when monitoring adherence over a short period of time (Osterberg & Blaschke, 2005; Velligan et al., 2006; Rijcken et al., 2004). Pill counts may overestimate adherence and can also be affected by the use of old pills (Osterberg & Blaschke, 2005; Velligan et al., 2006; Wright, 1993). Finally, electronic monitoring is based on the assumption that patients take their medication (and the right dose) when they open a bottle of pills. Nevertheless it is generally accepted that electronic monitoring is the best available measure of adherence (Osterberg & Blaschke, 2005; Wright, 1993; Byerly et al., 2007; Cramer, 2001; Diaz et al., 2001; Nakonezny et al., 2008; Nichol et al., 1999), and that it can be used in patients with severe mental illness (Diaz et al., 2001).

Velligan et al. (2006) reviewed adherence measures in 161 studies of adherence to oral antipsychotics between 1970 and 2006 and concluded that subjective methods are used in 75% of studies. This is no surprise since subjective instruments are cheap and easy to use. Previous studies have indicated, however, that the validity of these instruments

is generally poor. Assessments made by significant others depend on the degree of involvement with the patient and may be based largely on observed clinical outcome. Several studies consistently showed that clinician reports are not good indicators of medication adherence (Byerly et al., 2005, 2007; Remington et al., 2007).

Self-report instruments have also often been found to be invalid (Velligan et al., 2006; Kikkert et al., 2008; Lam et al., 2003). This may be caused by several weaknesses: patients may not understand questions, or they may give socially desirable or untruthful responses (Osterberg & Blaschke, 2005). Responses may be influenced by interviewer skills. In addition, adherence instruments do not usually specify the agent they focus on but rather give an overall adherence score. The possible false assumption here is that patient adherence is the same for all prescribed agents. However, patients may, for instance, adhere to a benzodiazepine regimen but not to an antipsychotic regimen (Piette et al., 2007). Several self-report instruments do not inquire about the amount of consumed medication and focus on related issues such as medication attitudes and present or previous experience. As a result, the relation between subjective adherence rates, often reported on 3 to 7-point Likert-type scales (Velligan et al., 2006), and the actual amount of medication consumed is obscure, making it difficult to compare study results. If questions are more straightforward, patients usually have to rate their adherence on a 0-100 scale, which also leads to poor validity (Byerly et al., 2007; Remington et al., 2007). The validity of self-reporting seems, however, to improve if another approach is used: instead of asking patients to mark their adherence behaviour, Haynes et al. (1980) asked hypertension patients to report the average number of pills missed per day, week and month. The answers were closely correlated to pill counts. Stewart (1987) asked patients who visited their family physician how many doses they had missed in 10 days. The sensitivity and specificity of this question was good compared with pill counting. In a study of patients with hypertension, Choo et al. (1999) found that, the only one of a number of self-report items that correlated with electronic medication monitoring was the self-reported number of forgotten medication doses during one week. These studies indicate that asking patients to recall specific events when medication intake does not correspond with their prescription during a time frame may be an interesting approach for measuring adherence.

Recently, Byerly et al. (2008) reported on a new instrument: the Brief Adherence Rating Scale (BARS). This instrument is used to assess patients' knowledge of their medication regimen, and patients are asked to report the number of days on which they fail to take some or all of their medication.

At the same time, and independently of the development of the BARS, our research group developed a new adherence instrument: the Inventory of Medication Intake (IMI). Although developed independently, the BARS and the IMI share the same basic principles. The IMI was constructed to assess the intake of medication based on a brief interview with the patient, overcoming some of the problems mentioned above. The key principle of this instrument is that patients are asked directly about their medication intake over a specified period of time.

The aim of this study is to validate the IMI in chronic outpatients with schizophrenia or a psychotic disorder. The results will be compared with four other frequently used subjective adherence measures: the Medication Adherence Rating Scale (MARS), the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), the Compliance Rating Scale (CRS) and a simple 100-point clinician estimate of medication adherence. The electronic Medication Event Monitoring System (MEMS) will be used as the gold standard to validate all the other measures. We will calculate the correlation with the MEMS for all measures, as well as sensitivity and specificity, and positive and negative predictive values.

Methods

Patients

Patients were recruited in community mental health care teams. The inclusion criteria were a diagnosis of schizophrenia, at least two years of continuous psychiatric care, sufficient command of the Dutch language, outpatient and prescribed oral atypical antipsychotic medication for at least the following 6 months. The study was approved by the Medical Ethics Committee and all patients gave informed consent.

Procedure

We selected three community mental health care teams serving a total of 600 outpatients. On the basis of case files, we selected patients who met the inclusion criteria. Treating clinicians were informed and asked for their approval to approach clients. Patients for whom approval was received were invited in alphabetical order to participate in our study. A research assistant visited the patients once they had given written informed consent. During the first visit, the IMI was completed and patients were instructed to use the MEMS container for the next three weeks. After three weeks, during the second visit,

the MEMS container was collected and the IMI was completed, together with two other self-report adherence instruments, and an exit interview was conducted. Mental health nurses were asked to complete a short questionnaire about their patients' adherence to antipsychotic medication. Records of actual medication prescriptions were obtained from case files. The patients, the research assistant and the mental health nurses were not aware of MEMS-generated results.

Instruments

The Inventory of Medication Intake (IMI)

The IMI is based on self-reporting and is administered as a structured interview which takes approximately 7 minutes and does not require special training or knowledge. Some experience in interviewing patients with schizophrenia is, however, recommended. In a previous study, we assessed the efficacy of adherence therapy based on motivational interviewing techniques in patients with schizophrenia (Gray et al., 2006). We found that if an understanding, open-minded atmosphere was created, patients were usually frank about how they used their medication. Assessments were therefore preceded by a compulsory introduction aimed at promoting a non-judgemental and understanding atmosphere with a view to reducing patients' hesitancy to be frank. During this introduction, the patients were told that, for anyone who is prescribed medication for a longer period of time, it is quite common to deviate from their prescription because people may feel more comfortable using more or less medication. It was explained that it is understandable for medication to be forgotten sometimes or for a mistake to be made. We also told patients that, if they told us that they had deliberately used more or less medication, they would not have to explain their reasons to us. Finally, we explained that any information we collected was confidential and would not be reported to their clinician or key worker.

After the introduction, patients were asked to report their medication regimen for all prescribed medication (see Appendix 1). Throughout the questionnaire, the number of pills was chosen as the unit of reference rather than the dose or the general expression 'medication'. We expected this to be the easiest approach for patients and to generate the most accurate responses. Patients were then asked to report the number of days on which they had not taken that agent at all over the past three weeks. Three weeks was considered the maximum period for which most patients would be able to reconstruct their medication intake. Finally, they were asked to state the number of days on which their intake was more or less than prescribed, and how many pills they had taken on

the days they had not followed their prescription. Patients were asked whether their individual deviations from the prescription were intentional or accidental in each case. This was repeated for each prescribed psychotropic medication. The research assistant noted the answers.

Other self-report adherence instruments

The *Medication Adherence Questionnaire* (MAQ) consists of four yes/no questions and addresses ways in which patients may fail to take their prescribed medication (Morisky et al., 1986). Patients with a score ≤3 on the MAQ were considered non-adherent (George et al., 2000; et al., 1986; Rith & Ivey, 2005).

The *Drug Attitude Inventory* (DAI) asks patients to decide whether ten yes/no statements reflecting experiences, attitudes and beliefs about medication apply to them. Patients were labelled non-adherent if the sum of the negative items was greater or equal to the sum of the positive items (Hogan et al., 1983).

On the basis of the MAQ and six items from the DAI, it was possible to compute a third adherence scale: the Medication Adherence Rating Scale (MARS) (Thompson et al., 2000). A higher score on the MAQ, DAI and MARS indicates better adherence.

Clinician reports

Although mental health nurses do not prescribe medication in our system, they have the most frequent contacts with patients. We therefore asked the nurses to estimate, for the antipsychotic medication only, the percentage of pills taken by the patient during the three-week period. They were also asked to indicate how confident they were about this estimate by choosing a range of 10%, 20% or 30% either way as a confidence interval.

Nurses were also asked to rate adherence behaviour using the 7-point Compliance Rating Scale (CRS). For each score, a brief description of adherence behaviour was provided, ranging from complete refusal to active participation in medication treatment (Kemp et al., 1998). Patients with a score ~ 4 on the CRS were labelled non-adherent (Byerly et al., 2005; Kemp et al., 1998; Kemp & David, 1996; Mutsatsa et al., 2003).

MEMS

The *Medication Event Monitoring System* (MEMS) was used as the standard for validating all the other adherence instruments. The MEMS is an electronic device placed out of sight in the cap of a standard medication bottle. This cap registers the time and date of all openings of the medication bottle and is considered a valid indicator of medication intake

(Byerly et al., 2007; Diaz et al., 2001; Nakonezny et al., 2008). The medication bottle contained only the primary oral antipsychotic medication.

The research assistant helped patients to place their medication in the medication bottle and told them that they should take all the antipsychotic medication they wanted to use from this bottle. It was emphasised that participation in the study should not interfere with medication intake. Patients were told about the MEMS device. Although the medical ethics committee approved withholding information from patients about the MEMS mechanism, we were concerned about potential damage to patient trust if they found out independently. In addition, during a pilot study, we had found it difficult to instruct patients without informing them.

Analysis

We defined medication adherence as the proportion of medication intake to prescribed medication during the three-week period. MEMS adherence rates were based on the total number of openings, regardless of the time of opening. To account for errors in MEMS data we asked patients during an exit interview (a) whether all the antipsychotic medication consumed was taken from the medication bottle, (b) whether the medication bottle had been opened without any pills being taken, (c) how often the medication bottle was opened for refilling, and finally (d) whether there had been any changes in the medication prescription. This information was used to correct the MEMS data. Bottle openings for refilling were, for instance, removed from the final MEMS data file. IMI adherence rates were calculated using the self-reported medication intake based on questions 7, 9 and 10 of the IMI (see Appendix 1). Patients were considered adherent if their medication intake was between 80% and 110% of their prescribed antipsychotic medication. Patients using less than 20% of their prescribed medication were considered non-adherent. The remaining patients were classified as being partially adherent or, if they consumed more than 110%, as over-consumers.

A Pearson correlation was calculated between MEMS adherence rates and all other adherence instruments after we had checked whether the basic conditions had been met for this test. We also calculated univariate linear regression for the IMI. Specificity, sensitivity, positive and negative predictive values, and positive and negative likelihood ratios were calculated for all adherence instruments. Test-retest reliability was calculated using a Pearson correlation.

Results

A total of 124 patients who met the inclusion criteria were selected for participation. Of these patients, 38 refused to cooperate, and the medical health nurses of 27 patients decided that participation would be too stressful, or too difficult for them. Eight of the patients who refused were reluctant to use the MEMS device, twelve preferred to continue using their pill box, and the remaining patients did not give a reason. A total of 59 patients agreed to participate in the study. The data of three patients were lost because the MEMS caps were lost. Another five patients did not understand the instructions and opened the MEMS container more often in order to 'count' medication as being taken. In all, the data of 51 patients (37 males and 14 females) were included in the analysis (see Table 1).

Correlation of IMI with MEMS

We first checked whether the medication regimen, as reported by the patient on the IMI, matched the actual prescription. In the case of nine patients, we found that the prescription reported by the patients on the IMI was different from the actual prescription. Seven patients were mistaken about the dosage (mg) of their prescribed medication. Another two patients were mistaken about the number of pills prescribed a day. Where there were differences between reported and actual medication prescription, the actual prescription was used to compute levels of adherence.

According to the MEMS, 25.5% of patients were not fully adherent during the measurement period. Average medication intake deviated 11.9% (SD=17.3) from medication prescription. According to the IMI, 7.8% of patients were not fully adherent and the average deviation was 3.9% (SD=10.4) (see Table 2).

Table 1. Characteristics of included patients (n=51)

Characteristic		
Age, mean (SD)	44.8	(9.3)
Sex, male, N (%)	37	(72.5)
Diagnosis, N (%)		
Schizophrenia	47	(92.2)
Psychotic disorder	4	(7.8)
GAF score, mean (SD)	50.8	(10.7)
Level of education, N (%)		
Less than high school	6	(11.8)
High school	19	(37.3)
Higher education	6	(11.8)
Unknown	20	(39.2)
Cultural background, N (%)		
Dutch	32	(62.7)
African	5	(9.8)
Caribbean, Surinam	5	(9.8)
Other Europe	4	(7.8)
Asian	2	(3.9)
Unknown	3	(5.9)

Table 2. Adherence rates according to the MEMS and the IMI (n=51)

Adherence categories	**MEMS**		**IMI**	
	N	**%**	**N**	**%**
0% – 20% (non-adherent)	0		0	
21% – 80% (partial adherent)	11	21.6	4	7.8
81% – 110% (adherent)	38	74.5	47	92.2
110% –140% (over-consumption)	2	3.9	0	

Intent or mistake

Patients were asked to report, for each day they deviated from their medication prescription, whether they had done so deliberately or by mistake. A total of 13 patients said they had deviated on between 1 and 6 days from their prescription because they had forgotten their medication or made a mistake (e.g. accidentally taken an extra dose). One patient deliberately deviated from his prescription on 13 days.

Test-retest reliability

The correlation between reported adherence rates on the IMI at the first and second visits was 0.998, p=0.000. Assuming patients did not change their adherence behaviour, this indicates high test-retest reliability.

Correlation with IMI

Table 3 shows the mean adherence rates derived from the various adherence instruments and their correlation with MEMS. We checked for all instruments whether the basic assumptions for a Pearson correlation had been met. The correlation between the MEMS and IMI adherence rates was 0.445 (p=0.001). Correlation coefficients for the other instruments were lower and ranged from -0.067 to 0.169. We performed a linear regression with MEMS as the dependent variable and IMI as the independent variable and found an R2 of 0.20, and a β of 0.81 (p=0.001).

Specificity and sensitivity

Using a cut-off point for the MEMS adherence rate of 80%, sensitivity and specificity were calculated for all adherence instruments (Table 3). This cut-off point of 80% is the most frequently used cut-off criterion in adherence research for patients with schizophrenia (Valenstein et al., 2002). Optimal sensitivity for the IMI was found with a cut-off point of 89.0. Sensitivity was 36.4 and specificity was 97.5, with an area under the curve of 59.5. The positive predictive value was 80.0, and the negative predictive value was 84.8. PPV and NPV were influenced by the prevalence of adherent and non-adherent patients in the sample and so we also present the PLR and NLR, which indicate that the IMI performs better than the other instruments.

To calculate sensitivity and specificity for the MAQ, DAI and CRS we used standard cut-off criteria derived from the literature. For the MARS and clinician estimates, we adopted cut-off points of 8.9 and 98.5 respectively, since this resulted in the best possible sensitivity with acceptable specificity. Sensitivity for the various instruments varied from 10.0 to 70.0, and specificity ranged from 38.9 to 97.5.

Nurse estimates of the proportion of taken medication on a range from 0% to 100% correlated poorly with actual adherence rates according to the MEMS data. When nurses were asked to state a confidence interval for their adherence estimates, the majority (81.8%) thought their estimates would not be more than 10% inaccurate in either direction. Accounting for this confidence interval, actual adherence rates fell in 75.0% of cases within this confidence interval. Adherence was overestimated in 22.7% of cases, and underestimated in 2.3% of cases.

Table 3. Means for adherence instruments, and the relationship with MEMS (n=51)

	Range	Mean	SD	Correlation with MEMS		Sensitivity[1]	Specificity[2]	AUC[3]	PLR[4]	NLR[5]
				R	p					
IMI	0-100	96.1	10.4	0.445	0.001	36.4	97.5	59.5	14.56	0.65
MARS	0-10	7.8	1.7	0.169	0.261	70.0	38.9	53.1	1.15	0.77
MAQ	0-4	3.6	0.7	0.070	0.645	30.0	77.1	51.8	1.31	0.91
DAI	0-10	7.1	2.2	0.097	0.519	20.0	72.2	45.6	0.72	1.11
CRS	1-7	6.3	1.1	-0.067	0.659	10.0	94.4	38.3	1.79	0.95
Clinician estimate of adherence	0-100	95.5	7.2	0.083	0.594	50.0	67.6	56.5	1.54	0.74

[1] Probability that a non-adherent patient will be classified as non-adherent by the adherence instrument

[2] Probability that an adherent patient will be classified as adherent by the adherence instrument

[3] Area under the curve

[4] Positive likelihood ratio; ratio between the probability that a non-adherent patient will be classified as non-adherent by the adherence instrument, and the probability that a adherent patient will be classified as non-adherent by the adherence instrument [sensitivity/(1-specificity)]

[5] Negative likelihood ratio; ratio between the probability that a non-adherent patient will be classified as adherent by the adherence instrument, and the probability that a adherent patient will be classified as adherent by the adherence instrument [(1-sensitivity)/specificity]

Discussion

In this study, we assessed the feasibility of the IMI and validated the IMI using the MEMS as the gold standard. IMI feasibility was good, and administration of the instrument was easy, taking approximately 7 minutes. Even though the mean GAF score in our sample was 51, no-one found the questions difficult. We checked whether patients with lower GAF scores would make more errors in reconstructing their intake of medication and found no differences.

The adherence rates derived from the IMI refer exclusively to the proportion of consumed antipsychotic medication during the past three weeks. This makes the interpretation of the IMI straightforward and improves comparability, as recommended by Velligan et al. (2006).

With the IMI, we tried to improve on all existing subjective instruments by a) using a direct simple approach asking patients to report deviations from prescription, b) using

pills as a reference, c) focusing on one type of medication, d) creating a non-judgemental environment. The resulting IMI is, in our view, the best possible subjective instrument for assessing adherence. The IMI outperforms the other subjective adherence instruments in our study in terms of sensitivity, specificity, NPV, PPV, and PLR and NR. Even so, using 80% adherence on the MEMS as a cut off point for non-adherence, the IMI misses two-thirds of all non-adherent patients, resulting in a sensitivity of 36.4. This makes its validity questionable and raises the question whether subjective methods are an appropriate way of identifying non-adherent patients.

A few questions had been added to the IMI to gain some insight into patient adherence. Two patients were non-adherent because they erred in their interpretation of their medication prescription. We also found that most non-adherence is unintentional, although we must bear in mind that patients may not easily admit to deliberate non-adherence. However, if forgetting about medication is a major reason for non-adherence, it is likely that many deviations are not accounted for on the IMI, resulting in higher adherence rates. Finally, we found that 20.8% of all patients did not know or understand what their prescribed antipsychotic medication was for, or only took it because it was prescribed to them.

This study has limitations. In some respects, our patients may not have been representative for the entire population. They had, on average, high adherence rates. Valenstein et al. (2006) found that, at any one time, adherence was poor in 37% of patients (<0.8). In our sample, this was 22%. This may be caused by self-selection bias. Approximately half of all the selected patients were excluded. Furthermore, included patients were informed that their medication intake would be monitored. Although we stressed that this should not influence their behaviour and that they should use their medication as desired, we cannot exclude the possibility that patients were more aware of, or even compensated for, missed doses. We do not know how this affected our results. We can speculate that adherent patients are more forthcoming about their medication intake than non-adherent patients. If so, this may have had a positive impact on our results. We checked for this possibility and found no differences in correlation coefficients between the MEMS and the IMI for adherent and non-adherent patients. This may indicate that self-reports of non-adherent patients on the IMI are as valid as those from adherent patients.

In this study, patients were aware that information was confidential and not available to their treating clinicians. Depending on the therapeutic relationship, patients may be more or less hesitant to admit to deviations from their prescription. Although

administering the IMI in a clinical setting may be a good starting point for the discussion of medication use, further research will be needed to determine the validity of the IMI in such settings.

Recently, Byerly et al. (2008) reported on the BARS, an instrument quite similar to the IMI which was also administered by research assistants. Byerly et al. found a correlation coefficient with electronic medication monitoring (r=0.59) that was similar to our study, but they found higher sensitivity (73.1) and lower specificity (74.3) in sample of 61 patients with schizophrenia and schizoaffective disorder. Their study used a cut-off point of 70%. With the same cut-off point, the sensitivity and specificity of the IMI are 50.0 and 97.8 respectively. There are, however, some differences. Firstly, the BARS combines self-reporting with a clinician rating. The research associates estimated adherence rates on a visual analogue scale on the basis of information given by the patient. In the IMI, the self-reported information was used to compute the adherence rate in conjunction with the actual prescription. Secondly, Byerly et al. assessed patients more often and over a longer period of time. Finally, their sample included patients with schizoaffective disorders, more women, and fewer Caucasian patients. More importantly, however, the adherence rates in the sample of Byerly et al. were lower and more representative than in our sample.

Patients using atypical antipsychotics may be more adherent than users of conventional antipsychotics, but study results are not conclusive (Valenstein et al., 2004; Kahn et al., 2008; Lacro et al., 2002; Lieberman et al., 2005). Although there is no evidence to justify the assumption that the type of medication would have affected our results, we ensured that all patients in this study used atypical antipsychotic medication in order to improve the homogeneity of our sample.

Approximately one quarter of all adherence studies use non-validated adherence measures (Nichol et al., 1999). Nichol's study, as well as other studies, has shown that many measures, even though they are apparently valid, are poor indicators of medication adherence. Several studies, for instance, consistently showed that clinician reports are not valid. Nevertheless, this is the second most frequently used method in adherence research (Velligan et al., 2006). We advise researchers to refer exclusively to well described and validated instruments.

The use of the MEMS device has some drawbacks, as described by other researchers. It is not possible to check whether the right number of pills are taken each time the medication bottle is opened, and some of the MEMS caps were lost. In addition, we also found that the MEMS is quite difficult to use for some patients. Patients with

paranoid features were particularly reluctant to use the MEMS device. Others found it too confusing and, for instance, thought they had to press the counting device in the cap manually to count each pill taken.

The IMI is a feasible instrument but suffers from poor sensitivity. Depending on the cut-off point for the MEMS adherence rate, only 36% to 50% of non-adherent patients were detected by the IMI. Those who were labelled as non-adherent by the IMI were, however, labelled correctly in the majority of cases (80%) according to the MEMS.

In this study, IMI was superior to other, frequently-used, subjective measures of adherence. The IMI has a better correlation coefficient with MEMS and better positive predictive value. We therefore conclude that, if a quick, easy and cheap measure is required, the IMI should be used in combination with an objective measure such as electronic monitoring, pill counting, or refill rates and prescription records. Bearing in mind the more acceptable sensitivity and specificity characteristics found by Byerly et al. (2008) we conclude that further research into the validity of this method is necessary.

Researchers should continue to strive for better adherence measures. In this study, we hope to have demonstrated that sympathising with the difficult task of taking medication each and every day, and simply listening to patients, constitute an alternative way of acquiring valuable information.

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Appendix 1: Inventory of Medication Intake (IMI)

Instructions

This questionnaire should be administered in an interview with the patient.

Answers are noted on the form by the interviewer.

The questionnaire assumes that the medication prescription dictates daily intake. If medication has to be taken with a lower frequency, please note the timeframe (e.g. week or month) the dose refers to.

The following introduction must be used before each interview.

Introduction

"In the following questions I would like to ask you about the use of medication. Although medication is prescribed by clinicians, it is up to the patient to decide whether or not they want to use them.

We know from other patients that it is **difficult to comply** with a medication prescription and it is quite **common to deviate**. Patients may sometimes feel more comfortable when they **use more or less** medication than is prescribed to them. And it is also obvious that medication may sometimes be **forgotten** or that other **mistakes** may be made.

I am interested in **how much** medicine you have taken in the past **three weeks**. If you have taken more or less of the medicine than was prescribed to you, you **do not need to explain to me why**. Please try to remember how you managed your medicine in the **past three weeks**."

Questions

1.Are you being prescribed medication at the moment?	yes	No (*end interview)*
2. How many different drugs have been prescribed to you?	…….	
3. Can you tell me the names of these drugs?	*note in table below*	

Pursue only the agents of interest in the remainder of the questionnaire. Ask questions 4 to 11 for each agent separately. Note the answers to the following questions in the table below.

4. Can you tell me what [agent] is for?
5. According to your prescription, do you know how many pills of [agent] you need to take each day?
6. Do you know the dose of one pill?

7. In the past three weeks, on how many days have you not taken [agent] at all?
8. If so, had you forgotten your medicine or did you choose to not take it?

9. In the past three weeks, how many days did you take more or fewer pills than was prescribed to you in the past three weeks?
10. If so, how many pills of [agent] did you take on average on these days?
11. Was this by mistake or deliberate?

Continue with question 4 for the next agent

Table

	3. agent (name)	4. purpose	5. number of prescribed pills (pills/day)	6. dose (mg/pill)	7. number of days pills were not taken at all (days)	8. forgotten or deliberate (forgotten)	9. number of days a deviating dose was taken (days)	10. average number of pills on deviating days (pills/day)	11. mistake or deliberate (mistake)
1						yes no			yes no
2						yes no			yes no
3						yes no			yes no
4						yes no			yes no
5						yes no			yes no
6						yes no			yes no