Medication adherence in patients with schizophrenia: a means to an end
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Chapter 4

Assessment of Medication Adherence in Patients with Schizophrenia. The Achilles Heel of Adherence Research

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Abstract

Measuring medication adherence in patients with schizophrenia is difficult and lacks a gold standard. Consequently, a great number of different methods and instruments have been proposed. Although it has been assumed that they all measure medication adherence, this study demonstrates that instruments differ significantly. Using data from an international multisite study (N=329), we found that 3 questionnaires, designed to measure medication adherence and typical for instruments used in studies in patients with schizophrenia, do not agree in labeling patients as non-adherent. Further, they seem not to measure the same trait, are related to different established risk factors of non-adherence, and are only weakly related to these established risk factors of non-adherence. If these results are representative of the validity of other measures used in adherence research, this may have serious consequences for the interpretation of, and explanations for discrepancies found in the literature. Researchers should be aware of this problem and continue to combine objective and subjective methods in the hope of increasing the reliability and validity of measures of adherence.
Assessment of medication adherence

Introduction

Non-adherence or poor adherence is a major concern in the treatment of chronic conditions such as schizophrenia. It places patients at risk for exacerbation of symptoms, care needs, and hospitalization with major social and economic consequences (Ayuso-Gutierrez & del Rio Vega, 1997; Weiden & Olfson, 1995). Although this has been known for several decades and studied extensively, clinicians still face a large number of non-adherent patients and do not make consistent use of evidence based adherence interventions (Ostenberg & Blaschke, 2005).

A vast literature has been published on this topic and a wide variety of instruments and methods are used to measure medication adherence (Velligan et al., 2006). It is unknown how these different measures of adherence affect study results. They at least make comparisons between studies problematic. This is particularly relevant in studies that try to determine (non)adherence rates, detect risk factors for non-adherence, and establish efficacy of adherence interventions. Not surprisingly non-adherence rates reported in studies vary considerably. Cramer and Rosenheck (1998) found non-adherence rates ranging from 24% to 90%. Lacro et al. (2002) in their systematic review found non-adherence rates ranging from 4% to 72% while others concluded that a mean of 40% to 60% of patients with schizophrenia are believed to not adhere to their prescribed medication regimen (Nose et al., 2003; Young et al., 1986).

Systematic reviews on risk factors for non-adherence in patients with schizophrenia show a consistent influence of certain variables (insight and therapeutical alliance, for example), while study results for other variables such as age, gender, marital status, duration of illness, etc., are too inconsistent to draw a conclusion regarding their influence on adherence behavior (Lacro et al., 2002; Oehl et al., 2000; Perkins, 2002; Pinikahana et al., 2002). Although it is unknown what causes these discrepancies, it has been argued that they might be attributed to different methods and instruments used to measure adherence, a problem which is not restricted to adherence measurements in schizophrenia (Nichol et al., 1999; Osterberg & Blaschke, 2005; Velligan et al., 2006).

Although the concept of medication adherence, defined as the degree to which medication is taken as prescribed, is relatively simple, measuring adherence behavior clearly is not. Adherence assessments can be divided in objective and subjective measures. Objective measures are blood, urine or hair concentrations, pharmacy records and electronic pill counts. Subjective measures rely on assessments made by the patient or a closely involved person such as a clinician, nurse, or relative using questionnaires or
interviews. In self-reports, patients are asked to rate their own adherence behavior or answer questions directly or indirectly related to medication use.

Reports from others usually rely on observed behavior such as clinical response, medication refusal, missed doses, regularity of visits, etc. Some studies combine a number of these methods to assess adherence rates. Lam et al. (2003) compared 3 different measures of adherence in patients with schizophrenia (plasma levels, pill count, and self-report) and found a remarkable poor agreement ranging from 0.17 to 0.28. In this study we will focus on the agreement of 3 adherence measures which are more similar in their approach.

In schizophrenia research approximately 75% of all studies rely on subjective measure (Velligan et al., 2006). Objective measures are often too complex, invasive, costly, or time-consuming. These subjective measures are, however, often poorly described, not validated, and are susceptible to error, misinterpretation, or distortion (Kane, 1983; Nichol et al., 1999; Nose et al., 2003; Otterberg & Blaschke, 2005; Velligan et al., 2006). Consequently, for the majority of instruments it is not known how validly they measure medication adherence. In the literature study, results are nevertheless interpreted as if they measured the same concept. If, however, the different instruments measure different concepts, this would partly explain between-study variability in findings and conclusions.

In this article, we will explore 3 subjective adherence instruments (1 clinician rated and 2 patient rated) frequently used in adherence studies in schizophrenia. We will examine: (a) to what extent these instruments agree in labeling patients as non-adherent, (b) to what extent these instruments measure the same concept, and (c) how they are related to established risk factors for non-adherence.

**Methods**

**Study Design**

This study uses baseline data from the Quality of Life Following Adherence Therapy for People Disabled by Schizophrenia and their Carers (QUATRO) study, an international randomized controlled trial assessing the efficacy of Adherence Therapy in patients with schizophrenia.

All patients that fulfilled the inclusion criteria and gave written informed consent completed a number of questionnaires and were interviewed before randomization and start of the adherence intervention (Gray et al., 2006).
Participants
Patients were recruited in 4 European cities: London (United Kingdom), Verona (Italy), Leipzig (Germany), and Amsterdam (The Netherlands). Inclusion criteria were (a) clinical diagnosis of schizophrenia according to ICD-10 criteria, confirmed by a research diagnosis of schizophrenia using the Item Group checklist (IGC) of the Schedule for Clinical Assessment in Neuropsychiatry (Wing et al., 1990), (b) in need of maintenance antipsychotic treatment for at least one year after entry into the study, and (c) evidence of clinical instability in the previous year, defined by one or more of the following: at least one hospital admission on clinical (mental health) grounds, a change in antipsychotic medication, increased frequency of planned or actual contact, indications of clinical instability from relatives, carers or clinical team. Exclusion criteria were (a) moderate or severe learning disabilities, (b) organic brain disorders, and (c) treatment by forensic psychiatric services.

Adherence Instruments
Subjective measures differ greatly among studies. Often unspecified and ad hoc measures are used (Velligan et al., 2006). Only a limited number of standardized and established instruments are available. None of them is considered a (gold) standard. We selected 3 of these instruments for which some methodological evidence for the validity of these measures exists. The measures are typical for instruments used in studies in patients with schizophrenia and represent the way adherence is often operationalized: a self-report questionnaire (Medication Adherence Questionnaire, MAQ) (Morisky et al., 1986), a clinician rating of adherence (the Compliance Rating Scale, CRS) (Kemp & David, 1996), and a self-report questionnaire on drug attitudes (Drug Attitude Inventory, DAI) (Hogan et al., 1983).

The MAQ consists of 4 yes/no questions and addresses ways in which patients may fail to take their prescribed medication: forgetting, carelessness, stopping the drug when they feel better, and/or stopping the drug because they believe it makes them feel worse (Morisky et al., 1986). A higher score on the MAQ indicates less problems with medicine taking and good adherence behavior. The MAQ is applied to medical conditions including treatment for high blood pressure. Good internal consistency (α=0.61) have been demonstrated in a sample of 400 randomly selected patients who had been tested for high blood pressure. A factor analysis confirmed the unidimensionality of the scale. In a 5-year follow-up a significant positive correlation of 0.58 was found between the level of compliance measured by the MAQ and blood pressure control indicating good
validity of the MAQ (Morisky et al., 1986). In a study by Thompson et al. (2000) serum concentrations of a mood stabilizing drug (N=17) correlated 0.36 with the MAQ. George et al. (2000) compared the MAQ with the Medication Event Monitoring System (MEMS) in patients using tricyclic antidepressants and found sensitivity scores ranging from 72% to 84% and specificity scores ranging from 55% to 74%, depending on MEMS cut off level. Shalansky et al. (2004) concluded that the MAQ was a reasonable instrument in detecting non-adherent patients after comparing the MAQ with prescription refill data in patients using chronic cardiovascular medications (Shalansky et al., 2004).

The CRS is used to rate medication adherence on a 7-point scale. The CRS is scored by key workers. Complete refusal is scored 1, patients who partially refuse score 2, patients who reluctantly or passively accept treatment score 3, 4, or 5, and patients who moderately or actively accept treatment score 6 or 7. For each score a brief description of adherence behavior is provided in the questionnaire. Kemp et al. (1998) who described this instrument first, found a strong correlation between the CRS and self-reported measures of attitudes to drug treatment (DAI) (r=0.68). Byerly et al. (2005) however concluded that the clinicians’ ratings dramatically underestimated antipsychotic non-adherence. None of the patients who were determined as non-adherent according to MEMS data were detected by the CRS.

The DAI is a self-report measure comprising 10 yes/no statements reflecting patients’ experiences, attitudes, and beliefs about medication. Patients are asked to decide whether statements apply to them. Higher scores indicate a more positive attitude toward, and more positive experiences with medication. Hogan et al. (1983) validated the original 30-item DAI questionnaire on ratings made by the therapists about patients’ medication-taking behavior. Ten items were selected as having maximal group discrimination and classified 68% of the patients correctly as adherent or non-adherent compared with therapist’s ratings. Thompson et al. (2000) reported a correlation of 0.65 with serum concentrations of a mood stabilizing drug (N=17) and the DAI.

**Risk Factors**

We selected variables that have been identified as risk factors of non-adherence in at least 3 of 5 systematic reviews published between 1997 and 2002 (Fenton et al., 1997; Lacro et al., 2002; Oehl et al., 2000; Perkins, 2002; Pinikahana et al., 2002), and for which data were available. Given the attention they received in previous studies and their relevance for this topic, we decided to include side effects and medication characteristics in the analysis as well, although reports on their influence on adherence behavior are equivocal.
Included risk factors cover the following domains: (a) patient-related factors, (b) perceived beneficial medication effects, (c) psychopathology and functioning, (d) illness insight, (e) medication side effects, (f) medication type and dose, and (g) complexity of medication regimen.

**Patient-Related Factors**

Living situation was assessed with the European version of the Client Sociodemographic and Service Receipt Inventory (CSSRI-EU) (Chisholm et al., 2000). As an indicator of medication supervision and degree of family involvement, items of the Involvement Evaluation Questionnaire (IEQ-EU) were used (Schene et al., 1998; van Wijngaarden et al., 2000), assessing respectively how often the family ensured that the required medicine was taken, and their average weekly telephone or personal contact with the patient over the past 4 weeks. The IEQ-EU was completed by 166 carers, identified by patients. Remaining patients either did not consent to use carers information or could not identify a carer.

**Perceived Beneficial Medication Effects**

The sum score of 4 DAI items was used as an indicator of perceived beneficial effects. Selected items reflect feeling more relaxed, more normal, and having clearer thoughts when using medication and the feeling that medication can prevent one from getting sick.

**Psychopathology and Level of Functioning**

Level of psychopathology was assessed using the expanded Brief Psychiatric Rating Scale (BPRS-E). The BPRS-E consists of 24 items measuring the following dimensions: positive symptoms, negative symptoms, depression/ anxiety, and disorganization (Ruggeri et al., 2005). A higher score indicates more and more severe symptoms. Depression was assessed using the Calgary Depression Scale (CDS). The CDS is specifically developed for assessing depression in patients with schizophrenia by a 9-item structured interview (Addington et al., 1992). A high summary score on the CDS indicates depression. Level of functioning was assessed using the Global Assessment of Functioning (GAF) (Jones et al., 1995). A low score on the GAF indicates poor functioning. Two items from the Involvement Evaluation Questionnaire (IEQ-EU) were used as an indicator of substance abuse (van Wijngaarden et al., 2000). On these items carers indicated how often, during the past 4 weeks, they guarded the patient from using too much alcohol, and illegal drugs.
Insight
Insight was assessed with the expanded version of the Schedule for Assessment of Insight (SAI-E). The SAI-E is a semistructured interview measuring 3 dimensions of insight: awareness of illness, relabeling of psychotic symptoms, and treatment compliance (David, 1990; Kemp et al., 1998). Awareness of illness and relabeling of psychotic symptoms are based on self-report items. The subscale “treatment compliance” comprises 1 self-report item and 2 items in which the clinician rates the extent to which the patient accepts treatment and whether the patient unprompted asks for treatment. These clinician rated items were, however, excluded because they overlap with the concept of adherence. The remaining self-report item, in which the patient is asked whether he thinks his condition, or the problem resulting from it, warrants treatment is used as an indicator of awareness of need for treatment. Higher scores indicate a higher level of insight.

Medication Side Effects
The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) was used to measure side effects consisting of 51 items (Day et al., 1995). Day et al. (1995) validated the LUNSERS and found that it had a good test-retest reliability (r=0.811, p<0.001) and concurrent validity against the UKU side effect rating scale for psychotropic drugs (UKU) (r=0.828, p<0.001).

Medication Type and Dose
Information on type and dosage of prescribed antipsychotic medication was provided by the patient’s clinician. The prescribed daily dosage (PDD) was expressed as the proportion of the Defined Daily Dose (DDD) which is the international unit of drug utilization approved by the World Health Organization (WHO, 2003).

Complexity of Medication Regimen
Total number of psychotropic drugs prescribed to a patient and how often they needed to be taken each day were used as an index of the complexity of the medication regimen.

Data Analysis
Criteria to label patients as either adherent or non-adherent were derived from the literature. For the MAQ, patients with a score ≤3 are defined as non-adherent (George et al., 2000; Morisky et al., 1986; Roth & Ivey, 2005). For the CRS, patients with a score ≤4 are considered non-adherent (Byerly et al., 2005; Kemp & David, 1996; Kemp et al.,...
Assessment of medication adherence

1998; Mutsatsa et al., 2003). For the DAI, the sum of the negative items is subtracted from the sum of the positive items. If the resulting score is less than or equal to 0, patients are considered to be non-adherent (Hogan et al., 1983).

In the remaining analysis we used continuous adherence scores to increase statistical power. Associations between interval and dichotomous variables were assessed with Pearson product moment correlation. For ordinal variables a Spearman rank correlation was used. Correlations of subjectively rated variables were calculated using residual scores corrected for site differences. In Table 3 the level is set at 0.05. To partly correct for the increased family wise error in Table 4 as a result of multiple testing, we set the level at 0.005.

Potential risk factors for non-adherence were categorized into domains. For each domain the relation between each risk factor and the 3 adherence instruments was presented. The overall variance in adherence scores explained by all risk factors within each domain, and the overall variance explained by all risk factors that were significant at $p\leq 0.005$, were calculated and reported as the $R^2$ of a linear regression model.

Results

In the QUATRO study sample (N=409) eighty patients (20%) were in an inpatient setting (psychiatric or medical ward or in a 24-hour staffed overnight facility). These patients are excluded for further analysis to improve uniformity of our sample and to eliminate the effect of staff supervision on medication intake, which is often common practice in inpatient settings. Social and demographic characteristics are given in Table 1. Our sample (N=329) was predominantly middle aged, single, unemployed, male, and chronic, which is typical for patients under the care of community mental health teams.

Of 284 patients, for which a score on all 3 instruments was available, overall non-adherence rates for the MAQ, CRS, and DAI are 54.9%, 20.4%, and 14.1% respectively. Full consensus among the 3 instruments in labeling patients non-adherent is reached in approximately 4% of the patients. For the remaining 96% of the patients the 3 instruments give different outcomes, 117 patients (41.2%) are non-adherent according to only 1, and 52 patients (18.3%) are non-adherent according to 2 of the 3 instruments (Table 2).
Table 1. Sociodemographic, clinical, and adherence characteristics of patients (n=329)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sociodemographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.3</td>
<td>11.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>185</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity Caucasian</td>
<td>254</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single / unmarried</td>
<td>285</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paid or self employed</td>
<td>56</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living alone (with/without children)</td>
<td>156</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years antipsychotic(s) prescribed</td>
<td>13.6</td>
<td>9.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS; positive symptom subscale</td>
<td>12.2</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS; negative symptom subscale</td>
<td>10.7</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS; depression/anxiety subscale</td>
<td>13.1</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS; disorganization subscale</td>
<td>12.5</td>
<td>3.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ sum score (0-4)</td>
<td>2.89</td>
<td>1.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRS (1-7)</td>
<td>5.37</td>
<td>1.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAI sum score (0-10)</td>
<td>6.71</td>
<td>2.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Although all 3 instruments were developed and used to detect non-adherent patients, Table 2 and Figure 1 demonstrate the limited overlap in patients identified as non-adherent and show the differences in non-adherence rates. It is possible that this is due to using dichotomous scores that are based on different cut off criteria or interpretations of non-adherence. We therefore performed a Pearson product moment correlation to examine the relation between the total scores on the instruments (Table 3).

Again we found a poor overlap between the 3 instruments. The highest correlation coefficient was found between the CRS and the DAI (r=0.30; p<0.05), which is approximately equivalent to 9% explained variance. The low correlations do not exclude the possibility that one of these instruments is a valid measure of adherence behavior. In this case this instrument should, however, be related to established risk factors for medication non-adherence (Table 4).

All correlation coefficients of the 3 instruments with established risk factors were relatively low. Risk factors for which we found a statistically significant (though modest)
correlation were perceiving little or few positive effects of the medication, severity of depressive/anxiety symptoms, lower level of functioning, and poor insight.

**Table 2.** Patients labeled non-adherent according to the MAQ, CRS, DAI, or a combination of these instruments (n=284)

<table>
<thead>
<tr>
<th>Non-adherent according to</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>One instrument</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ</td>
<td>97</td>
<td>34.2</td>
</tr>
<tr>
<td>CRS</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>DAI</td>
<td>10</td>
<td>3.5</td>
</tr>
<tr>
<td>Total</td>
<td>117</td>
<td>41.2</td>
</tr>
<tr>
<td>Two instruments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ – CRS</td>
<td>33</td>
<td>11.6</td>
</tr>
<tr>
<td>MAQ – DAI</td>
<td>15</td>
<td>5.3</td>
</tr>
<tr>
<td>CRS – DAI</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>18.3</td>
</tr>
<tr>
<td>Three instruments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAQ – CRS – DAI</td>
<td>11</td>
<td>3.9</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**Figure 1.** Venn diagram representing the proportional overlap of the instruments in labeling patients non-adherent according to the MAQ, CRS, and DAI. Numbers present the size of each area in percentages (in contrast to Table 2 the denominator of the percentages in this diagram are the 180 patients labeled by at least one of the instruments as non-adherent).
### Table 3. Correlation coefficients for adherence measures (n=329)

<table>
<thead>
<tr>
<th></th>
<th>MAQ n</th>
<th>CRS n</th>
<th>DAI n</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAQ –</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CRS 0.25</td>
<td>295</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DAI 0.21</td>
<td>304</td>
<td>0.30</td>
<td>289</td>
</tr>
</tbody>
</table>

1 Boldface indicates p<0.05

### Table 4. Correlation coefficients of risk factors with adherence measures and explained variance \( R^2 \) for each domain and significant related variables (n=329)

<table>
<thead>
<tr>
<th>Patient-related factors</th>
<th>MAQ n</th>
<th>CRS n</th>
<th>DAI n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living situation (alone / with others)</td>
<td>-0.10</td>
<td>-0.04</td>
<td>0.05</td>
</tr>
<tr>
<td>Medication supervision by carer (IEQ-EU)</td>
<td>-0.06</td>
<td>-0.19</td>
<td>-0.15</td>
</tr>
<tr>
<td>Family involvement (IEQ-EU)</td>
<td>0.17</td>
<td>0.02</td>
<td>-0.01</td>
</tr>
<tr>
<td>( R^2 ) for patient-related factors</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Perceived beneficial medication effect</td>
<td>0.11</td>
<td>0.22</td>
<td>-</td>
</tr>
<tr>
<td>( R^2 ) for perceived beneficial medication effect</td>
<td>0.01</td>
<td>0.05</td>
<td>0.29</td>
</tr>
<tr>
<td>Psychopathology and functioning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPRS; positive symptom subscale</td>
<td>-0.13</td>
<td>-0.08</td>
<td>-0.12</td>
</tr>
<tr>
<td>BPRS; negative symptom subscale</td>
<td>-0.02</td>
<td>-0.06</td>
<td>-0.15</td>
</tr>
<tr>
<td>BPRS; depression/anxiety subscale</td>
<td>-0.16</td>
<td>-0.02</td>
<td>-0.11</td>
</tr>
<tr>
<td>BPRS; disorganization subscale</td>
<td>-0.02</td>
<td>-0.08</td>
<td>-0.08</td>
</tr>
<tr>
<td>CDS; total score</td>
<td>-0.13</td>
<td>-0.03</td>
<td>-0.22</td>
</tr>
<tr>
<td>GAF</td>
<td>0.13</td>
<td>0.24</td>
<td>0.30</td>
</tr>
<tr>
<td>Substance abuse (IEQ-EU)</td>
<td>-0.12</td>
<td>-0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>( R^2 ) for psychopathology and functioning</td>
<td>0.04</td>
<td>0.06</td>
<td>0.11</td>
</tr>
<tr>
<td>Illness insight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAI-E; symptom relabelling and hypothetical contradiction</td>
<td>0.05</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>SAI-E; illness awareness</td>
<td>0.05</td>
<td>0.22</td>
<td>0.18</td>
</tr>
<tr>
<td>SAI-E; awareness of need for treatment</td>
<td>0.19</td>
<td>0.33</td>
<td>0.32</td>
</tr>
<tr>
<td>( R^2 ) for illness insight</td>
<td>0.03</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>Medication side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LLUNERS; total score</td>
<td>0.03</td>
<td>0.02</td>
<td>-0.16</td>
</tr>
<tr>
<td>( R^2 ) for medication side effects</td>
<td>0.00</td>
<td>0.00</td>
<td>0.02</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Table 4. Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Medication type and dose</td>
</tr>
<tr>
<td>type of antipsychotic (atypical/classic)</td>
</tr>
<tr>
<td>dose (PDD/DDD ratio)</td>
</tr>
<tr>
<td>depot (yes/no)</td>
</tr>
<tr>
<td>R² for medication type and dose</td>
</tr>
<tr>
<td>Complexity of medication regimen</td>
</tr>
<tr>
<td>number of prescribed psychotropic agents</td>
</tr>
<tr>
<td>times a day patient needs to take medication</td>
</tr>
<tr>
<td>R² for complexity of medication regimen</td>
</tr>
<tr>
<td>R² for significant related risk factors</td>
</tr>
</tbody>
</table>

| a | To partly correct for the increased family wise error as a result of multiple testing, we set the alpha level at 0.005 |
| b | Analysis performed without medication supervision and family involvement since IEQ-EU data was only available for a restricted number of patients. R² for 'patient related factors' including all variables for the MAQ, CRS and DAI is respectively: 0.06 (N=136), 0.05 (N=130) and 0.02 (N=136) |
| c | Sum score of DAI items 4, 7, 9 and 10. Correlation coefficient and R² with the DAI is not calculated due to overlap |
| d | Analysis performed without substance abuse since IEQ-EU data was only available for a restricted number of patients. R² for 'psychopathology and functioning' including all variables for the MAQ, CRS and DAI is respectively; 0.14 (N=151), 0.10 (N=145) and 0.14 (N=151) |
| e | Risk factors included in analysis are: BPRS; depression/anxiety subscale, SAI-E; awareness of need for treatment |
| f | Risk factors included in analysis are: Perceived beneficial medication effect, GAF, SAI-E; symptom relabelling and hypothetical contradiction, SAI-E; illness awareness, SAI-E; awareness of need for treatment |
| g | Risk factors included in analysis are: CDS; total score, GAF, SAI-E; symptom relabelling and hypothetical contradiction, SAI-E; illness awareness, SAI-E; awareness of need for treatment |

For each domain, we assessed in a separate regression analysis the overall relationship between the risk factors pertaining to this domain and the 3 questionnaires. For all instruments explained variance was relatively low for all domains. An additional regression analysis was performed for each instrument incorporating only significantly correlated risk factors over all domains. This resulted in an R² of 0.06 for the MAQ, a R² of 0.13 for the CRS, and a R² of 0.16 for the DAI.

Discussion

To date a wide variety of instruments and methods are used to measure adherence. The aim of this article was to examine the extent to which 3 subjective instruments (1 clinician rated and 2 patient rated), frequently used to measure adherence in schizophrenia,
identify the same patients as non-adherent, measure the same concept, and how they relate to established risk factors for non-adherence. We found that there was little agreement among the instruments in labeling patients non-adherent, and they did not seem to measure the same concept. None of the instruments showed a clear relationship with established risk factors of non-adherence. Therefore, it is difficult to decide which one, if any, is an appropriate measure of adherence.

Our findings are highly relevant for studies that depend on a valid measure of medication adherence. Many different methods and instruments have been used in studies and it has been assumed that they all measure the same trait. We demonstrate that it may not be justified to assume this. We found poor overlap in 3 representative and frequently used measures. Although our results can not be generalized to other measures, it seems justified to question the validity of other, often not validated, instruments. Still most research uses one of these, or similar instruments. If adherence measures are not informative about actual medication intake, study conclusions are likely to be distorted and comparison with other studies is not possible. Given the importance of increasing our knowledge and evidence-based skills in adherence interventions, we should critically reconsider the use of inferior measures.

This study clearly indicates that conclusions regarding non-adherence rates or predictive factors of non-adherence can differ considerably if they are based on any of these 3 instruments alone. Therefore we conclude that the discrepancies found in literature are at least partly due to the heterogeneous methodology to measure medication adherence.

Although most variables used in this study have often been associated with adherence behavior, we were surprised by the weak relation with the adherence scales. Relatively few variables were significantly correlated with the adherence scales but more important, the correlation coefficients were rather low. We were not able to explain more then 20% of variance in adherence scores, a result that is not uncommon in this type of research. Such effect sizes are too small to be clinically relevant for the prediction or explanation of adherence behavior.

In this study we assumed that the adherence rates represent the degree of medication adherence and we expected at least some relation with established determinants of non-adherence. Given our results, we wonder if it is justified to assume a linear relation between medication intake and adherence rates on these instruments. Possibly these instruments are sensitive to deviant adherence behavior or negative medication attitudes. Using cutoff criteria might therefore be useful in identifying patients who are likely, or at risk for being non-adherent. We do, however, not know which patients are completely non-
adherent, skip a dose once a while, or "only" have ambivalent thoughts about medication. In research these instruments might therefore have limited value.

Concerning the low correlations between the adherence rates and risk factors in our study, there are 3 other issues we would like to raise. First, it has been argued that a patient's subjective perception of the effect of medication greatly influences adherence behavior (Adams & Scott, 2000; Marder 2005; Naber et al., 2005; Perkins et al., 2006). Although it is equally likely that established negative attitudes heighten sensitivity to adverse effects. Many variables, however, are based on clinician assessments. It might be more informative to focus on the patient's subjective ratings of perceived burden, family support, complexity of medication schedule, etc. (Ritsner et al., 2002). The LUNSERS for instance asks patients to rate how much they experienced a specific side effect instead of how much it bothered them. Second, other studies demonstrate that some patients attribute benefits to their medication that are not directly related to their illness (Adams & Howe, 1993; Chan, 1984). Patients might, for instance, fear that their children will be placed into care, financial consequences because of losing paid work, or loss of social support if they do not take their medication as prescribed. Although we appreciate that it is difficult in quantitative studies to incorporate such specific risk factors, they might be nonetheless important in understanding patients' behavior (Adams & Howe, 1993; Kikkert et al., 2006). Third, besides choosing relevant risk factors and a relevant perspective to measure them, one needs to consider what type of relation is expected. The statistical methods used in most studies assume linear relations. For some variables, however, it might be more appropriate to consider more complex relations or 2 directional relations. For example, adverse side effects might inhibit medication intake but are also likely to decline if medication intake is low, making it difficult, particularly in cross-sectional designs, to demonstrate a relation. This could perhaps also apply to other variables such as positive symptoms and quality of life, which might have a causal as well as a dependent relation with adherence.

According to a general accepted definition, patients are non-adherent if they do not fully follow medication prescription. This ignores a relevant distinction between completely and partly non-adherent patients. Skipping or forgetting a dose once every week is not the same as not taking medication at all. Grouping these patients together is likely to distort study results. Researchers should be more aware of the difference between measuring adherence behavior (degree of medication intake in reference to their prescription) and detecting non-adherent patients (identifying patients that do not fully comply with medication regimen or are at risk for being non-adherent).
We would like to argue that methods used to measure medication adherence should indicate the actual proportion of used medication, and if the patient uses more than one agent, refers to the agent of interest. This will increase comparability among studies. It will also allow researchers to define patients as non-adherent based on a pharmacological effective threshold; a minimum dose that will produce a clinically meaningful reduction of symptomatology. This may have more clinical relevance than the definition of non-adherence used up to date and may result in more valid study conclusions.

Although objective measures seem most appropriate to do this, they each have their limitations. Serum levels are invasive, costly, and require knowledge of individual pharmacokinetic characteristics. Pharmacy records can be informative but require an accurate administration system and only provide average adherence rates over longer periods of time (Rijcken et al., 2004). In other fields electronic devices which record openings of a pill bottle container (MEMS) has been suggested as a new gold standard and seem to be a reliable indicator of medication adherence (Nichol et al., 1999; Osterberg & Blaschke, 2005), practical in use in patients with schizophrenia (Diaz et al., 2001; Nakonezny & Byerly, 2006). MEMS is, however, relatively expensive and is sensitive to patient errors (Arnet and Haefeli, 2000; Bova et al., 2005). Researchers who are limited to using questionnaires might consider asking patients to report their own intake behavior over a limited period of time and combine this with information gathered from other sources such as a carer and/or key worker. Self-reports might, however, be susceptible to error and distortion. One of the main concerns is that patients might find it difficult to be frank about their medication intake. Creating a confidential, understanding, and nonjudgmental atmosphere is therefore important.

This study has limitations. Recruited patients met inclusion criteria including clinical instability in the previous 12 months. Although patient-related characteristics were representative for a population of patients with schizophrenia, this criterion might have affected our sample. Variables and adherence indexes used in this study were restricted by those used in the QUATRO study. For several variables we could not use appropriate measures but used proxies instead.

This study demonstrates that if we want to improve our understanding of adherence behavior in patients with schizophrenia, validated instruments are necessary that measure the degree of actual medication intake, as well as agreement among researchers to use them.
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References


Assessment of medication adherence


