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The predictive validity of subjective adherence measures in patients with schizophrenia

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Key words
schizophrenia, antipsychotics, medication adherence, adherence assessment, clinical course

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Abstract

Despite frequent use of subjective adherence measures in patients with schizophrenia as well as other chronic conditions, there are several reports that question the validity of these instruments. Three well known, representative subjective measures are the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), and the Compliance Rating Scale (CRS). In this study we explored the predictive validity of these instruments in a European sample of 119 stabilized outpatients with schizophrenia. Clinical outcome variables were relapse and admission to a psychiatric hospital during a follow-up period of 12 months. Results indicate that the predictive validity of all three measures was poor. The MAQ was the least problematic predictor for relapse (Nagelkerke $R^2 = 0.09$), and time to relapse ($R^2 = 0.07$) and had the best sensitivity for relapse (63.6%) as well as admission (87.5%). The MAQ and CRS were both moderate predictive for admission (Nagelkerke $R^2 = 0.21$, and $R^2 = 0.29$). We conclude that the validity of the instruments studied here is questionable and have limited clinical relevance. Given the feasibility and ease of most subjective instruments, researchers may be tempted to use them but should be aware of the serious drawbacks of these instruments. *Copyright © 2011 John Wiley & Sons, Ltd.*

Introduction

Studies have shown that medication use in patients with chronic conditions is generally poor (Sabaté, 2003). This is found for physical conditions such as cardiovascular diseases and HIV, but also in patients suffering from chronic mental health diseases such as psychotic disorders. This undermines the potential therapeutic effect of antipsychotic medication resulting in increased burden for patients, family, and professionals, as well as major economical costs.

Our knowledge concerning prevalence, efficacy of adherence interventions, and determinants of non-adherence is based on studies performed in the last

decades. These studies have one thing in common; their outcomes rely on a valid assessment of medication adherence. Several methods are available to measure medication adherence but the majority of adherence studies in schizophrenia, resort to subjective instruments, such as questionnaires or interviews that rely on self report or on assessments made by others (Velligan *et al.*, 2006). An advantage of these instruments is that they are cheap, easy to use and non intrusive. Unfortunately the instruments are often not validated, are susceptible to error, misinterpretation or distortion, and the quality of their description varies but is often poor (Nose *et al.*, 2003; Velligan *et al.*, 2006; Osterberg and Blaschke, 2005; Nichol *et al.*, 1999; Kane, 1983).

In a previous article (Kikkert *et al.*, 2008) we examined concurrent validity of three frequently used, subjective adherence measures; the Medication Adherence Questionnaire (MAQ), the Drug Attitude Inventory (DAI), and the Compliance Rating Scale (CRS) (Morisky *et al.*, 1986; Hogan *et al.*, 1983; Kemp *et al.*, 1998). Although all instruments claim to assess the degree of medication adherence, our results indicated that the instruments did not seem to measure the same concept. Also the overlap of patients labelled as non-adherent by the three instruments was limited. Based on these results we concluded that the concurrent validity was low and that it is very unlikely that all three validly assess adherence. This did however not preclude the possibility that one of these instruments is a valid measure of adherence.

Since these, and similar type of adherence measures, are so commonly used, this may have had an impact on the results of many studies. In this study we will further explore the validity of these instruments using the possible consequences of non-adherence; clinical deterioration and consequently psychiatric hospitalization as criterion. So far there is overwhelming evidence for the efficacy of antipsychotic medication (Ayuso-Gutierrez and del Rio Vega, 1997; Lieberman *et al.*, 2005; Keith and Kane, 2003; Morken *et al.*, 2008; Kahn *et al.*, 2008). Sub-therapeutic intake of medication is related to exacerbation of symptoms and relapse (Weiden and Zygmunt, 1997; Fenton *et al.*, 1997; Robinson *et al.*, 1999), and is the most important determinant for relapse in first episode psychosis patients (Malla *et al.*, 2006).

A secondary, clinically relevant effect of adherence might be admission during a follow-up period. In comparison to relapse, the effect of non-adherence on admission is influenced by circumstantial factors such as patient characteristics (e.g. patient preference), social characteristics (e.g. family support and living conditions) and (mental) health care characteristics (e.g. number of beds available, policy, outpatient treatment facilities). Therefore not all patients that relapse will also be admitted to a psychiatric hospital. Nevertheless, several large scale studies using pharmacy data or electronic medication monitoring as an indicator of medication adherence showed that non-adherent patients had higher admission rates (Valenstein *et al.*, 2002; Weiden *et al.*, 2004; Gilmer *et al.*, 2004; Diaz *et al.*, 2001; Eaddy *et al.*, 2005).

Some studies evaluated relapse or admission as outcome variable; in this study we are able to evaluate relapse, as well as admission of 119 stabilized outpatients with schizophrenia over a 12 month follow-up period. The aim of this study is to determine the predictive validity of three often used measures of adherence, the MAQ, DAI and CRS. Clinical outcome will be defined in our study as (a) risk of relapse and admission, and (b) time to relapse and admission.

Methods

Study design

Data used in this study was collected during the QUATRO study (Quality of life following adherence therapy for people disabled by schizophrenia and their carers), an international randomized controlled trial assessing the efficacy of Adherence Therapy in patients with schizophrenia (Gray *et al.*, 2006). The study was approved by all four local institutional medical ethical committees. During this study assessments were conducted at baseline and after 12 months. Ratings assessed at baseline were used in this study together with data on relapse and hospitalization during the 12 month follow-up period.

Participants

Patients were recruited in four European cities: London (UK), Verona (Italy), Leipzig (Germany) and Amsterdam (the Netherlands). Inclusion criteria were: (1) clinical diagnosis of schizophrenia according to the International Classification of Diseases (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), (2) in need of maintenance antipsychotic treatment for at least one year after entry into the study, and (3) evidence of clinical instability in the previous year (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: (1) moderate or severe learning

disabilities, (2) organic brain disorders and (3) treatment by forensic psychiatric services.

Approximately one third of patients are treatment resistant (Conley and Kelly, 2001; Kane 1996, 1999), ranging from persistent disabling symptoms despite adequate trials of medication, up to the absence of any medication benefit. For treatment resistant patients the assumed causal relation between medication adherence and relapse does not apply. In this study only outpatients, free of positive symptoms during the time of assessment were included for analysis. This ruled out the inclusion of treatment resistant patients. It also enabled us to examine the risk of relapse and psychiatric admission. The effect of antipsychotic medication on negative symptoms is limited and was therefore not incorporated as selection criterion or outcome variable. In the QUATRO study, there were no differences found between the treatment and control group on any of the outcome variables such as; the score on the MAQ, DAI and CRS, the risk for relapse or hospitalization, psychopathology as measured with the Expanded Brief Psychiatric Rating Scale (BPRS-E), or insight as measured with the expanded version of the Schedule for Assessment of Insight (SAI-E) (Gray *et al.*, 2006). All patients were therefore considered eligible for this study and treatment arm was not incorporated as a confounder.

After screening, 917 patients from four European countries were found eligible for the QUATRO study. Approximately a third of these patients ($N = 366$) refused to participate, and 142 patients could not be included for other reasons (Gray *et al.*, 2006). Out of the 409 included patients in the QUATRO study analysis in this study were based on 119 stabilized outpatients with schizophrenia who gave written informed consent. At baseline, 80 patients stayed in an inpatient setting or psychiatric hospital, and 148 outpatients were psychotic. A patient was rated psychotic if moderate to extremely severe positive symptoms, according to the BPRS-E, were present for at least one week. This was rated by the clinician. Finally, 62 patients were excluded for analysis because their clinical course data was incomplete (covered < 90% of the follow-up period).

Instruments

All instruments were administered once at baseline. Starting at baseline, clinical course was recorded during the follow-up period of 12 months.

Clinical course rating

Although there are no clear criteria for relapse, in accordance with Johnstone's (1992) definition, we defined relapse in this paper as reappearance of positive symptoms. For this purpose we used an instrument which was constructed to identify clinical course patterns of patients (Burti *et al.*, 2009). Clinicians were asked to rate if a patient was psychotic for each quarter of a month. Clinical course ratings were given for the entire follow-up period of 12 months. As described earlier, patients were rated psychotic if moderate to extremely severe positive symptoms, according to the BPRS-E, were present for at least one week. Psychotic episodes were considered separate if they were interrupted by a non-psychotic period of at least one month. Admissions to a psychiatric hospital were scored similarly on this instrument. Hospital admissions were considered separate if the time between two admissions was at least half a month (Burti *et al.*, 2009).

Adherence instruments

For each patient adherence was assessed with two self-report scales, the MAQ and the DAI, and one clinician rated adherence scale, the CRS.

The MAQ consists of four 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 better adherence behaviour.

The DAI is a self-report measure comprising 10 yes/no statements reflecting patients' experiences, attitudes and beliefs about medication. This 10-items version of the DAI was designed to assess medication adherence in patients with schizophrenia. Based on a validation study, 10 items were selected from the original 30 DAI-items as having maximal group discrimination of adherent and non-adherent patients (Hogan *et al.*, 1983). Patients are asked to decide whether statements apply to them. Higher scores indicate a more positive attitude towards medication, and better adherence behaviour.

The CRS is used to rate medication adherence on a seven-point scale. The CRS is scored by key workers. Complete refusal is rated one, patients who partially refuse score two, patients who reluctantly or passively accept treatment score three, four or five and patients who moderately or actively accept treatment score six or seven. For each score a brief description of adherence behaviour is provided in the questionnaire. A detailed description of statistical characteristics of these instruments is given in Kikkert *et al.* (2008).

For some analysis we classified patients as adherent or non-adherent using standard cut off criteria if available. For the MAQ, patients with a score ≤3 are defined as non-adherent (Morisky *et al.*, 1986; George *et al.*, 2000; Roth and Ivey, 2005). For the CRS, patients with a score ≤4 are considered non-adherent (Kemp and David, 1996; Byerly *et al.*, 2005; Kemp *et al.*, 1998; Mutsatsa *et al.*, 2003). For the DAI, the sum of the negative items are subtracted from the sum of the positive items. If the resulting score is less than or equal to zero, patients are considered to be non-adherent (Hogan *et al.*, 1983).

Other instruments

Other instruments used in this study were:

- the BPRS-E: this instrument consists of 24 items measuring the following dimensions; positive symptoms, negative symptoms, depression/anxiety and disorganization (Ruggeri *et al.*, 2005).
- the SAI-E: this is a semi-structured interview measuring three dimensions of insight: awareness of illness, relabeling of psychotic symptoms and treatment compliance (Kemp *et al.*, 1998; David, 1990). Finally, information on type and dosage of prescribed antipsychotic medication was provided by the patient's clinician.

Analysis

We explored sensitivity and specificity of the three instruments for relapse and psychiatric admission. Logistic regression analyses were used to study the relation between the continuous adherence ratings at baseline and psychotic relapse, and psychiatric admission during the follow-up period. We used a Cox Regression analysis to explore time to relapse and time to admission. Before Cox Regressions were performed we formally tested the proportional hazard assumption by adding an intervention by time interaction term to the regression model (Kleinbaum, 1990). None of the regression coefficients of this interaction term were statistically significant. Consequently, the proportional hazard assumption was met. To correct for multiple testing alpha was set at 0.017.

In the regression analyses a number of potential confounders were included as covariates. These confounders were all variables determined as risk factor for non-adherence based on literature reviews. For a detailed description see our previous paper (Kikkert *et al.*, 2008). Potential confounders were; living situation, medication efficacy, psychopathology, functioning, illness insight, medication side effects, type of antipsychotic (first or second generation, and depot), antipsychotic dose and frequency, and number of prescribed psychotropic agents. Based on the change-in-estimate strategy (Rothman and Greenland, 1998; Maldonado and Greenland, 1993; Sonis, 1998), confounders were included in the analysis if, when added to the Cox Regression model, the odds ratio for any of the adherence instruments changed more than 10%. Positive symptoms (measured with the BPRS-E) fulfilled this criterion but was not included as a confounder because we considered it part of the causal pathway between adherence and outcome. The following confounders were included: negative symptoms (subscale negative symptoms of the BPRS-E), insight; symptom relabeling and hypothetical contradiction (factor 1 of the SAI-E), insight; illness awareness (factor 2 of the SAI-E), and depot medication.

Results

Social-demographic characteristics and clinical outcomes for all included patients are shown in Table 1. Patients were middle aged, a slight majority was male, and relatively few were employed or married. On average patient's had been prescribed antipsychotic medication for approximately 13 years. The sample in this study showed no differences compared to the remaining outpatients in the QUATRO study on any of the socio-demographic characteristics, except for ethnicity. In our sample we had less Caucasians (63.0%) compared to the remaining outpatients in the QUATRO sample (85.2%). We also found that our sample had less severe psychiatric symptoms (mean BPRS-E total score of 38.4 compared with 48.4) which is probably due to excluding patients who were psychotic at baseline. Compared with the characteristics of more then 8000 outpatients with schizophrenia in two other European multicentre studies; the SOHO study (Haro *et al.*, 2006) and the EPSILON study (Ruggeri *et al.*, 2005), characteristics of our sample showed no differences. We therefore conclude that patients in this study form a representative sample of stabilized Western European outpatients with schizophrenia who had been clinically instable in the previous year.

During the 12-month follow-up period, 57 (48%) patients experienced psychotic symptoms severe enough to define it a relapse. On average, the monthly relapse rate was 5.3%. Each quarter 15 patients (13%) relapsed, except for the last quarter in which 12 patients relapsed (10%). Most patients (79%) who experienced a psychotic period had only one episode, and 18% had two episodes. Two patients had respectively three and five separate psychotic episodes. Out of the 57 patients with a relapse, 16 (28%)

Table 1 Characteristics of sample ($N = 119$)

Age, mean (standard deviation, SD)	40.7	(11.66)
Male, *N* (%)	68	(57.1%)
Ethnicity, Caucasian, *N* (%)	75	(63.0%)
Single/unmarried, *N* (%)	107	(89.9%)
Paid or self employed, *N* (%)	20	(16.8%)
Living alone, with/without children, *N* (%)	68	(54.0%)
Years antipsychotic(s) prescribed, mean (SD)	13.17	(9.92)
Highest completed level of education, *N* (%)		
Primary education or less	20	(16.9%)
Secondary education	58	(49.2%)
Tertiary/further education	40	(33.9%)
BPRS-E total score, mean (SD)	38.36	(12.04)
Psychotic relapse during follow up, *N* (%)	57	(47.9%)
Number of separate psychotic episodes, mean (SD) ($N = 57$)	1.28	(0.67)
Duration between baseline and (first) episode in months, mean (SD) ($N = 57$)	6.10	(3.26)
Duration of (first) psychotic episode in months, mean (SD) ($N = 57$)	2.05	(1.81)
Hospitalized during follow up, *N* (%)	16	(13.4%)
Number of admissions, mean (SD) ($N = 16$)	1.25	(0.58)
Duration between baseline and (first) admission in months, mean (SD) ($N = 16$)	6.08	(3.29)
Duration of (first) admission in months, mean (SD) ($N = 16$)	3.24	(2.60)

Table 2 Prediction of relapse and admission

	β	SE	Wald	Sig.	Exp(β)	95% CI	Nagelkerke[b]	*N*	–2 log likelihood[b]
Relapse[a]									
MAQ	–0.613	0.231	7.054	0.008	0.542	0.345–0.852	0.092	93	109.000
DAI	–0.120	0.106	1.296	0.255	0.887	0.721–1.091	0.059	92	111.178
CRS	–0.345	0.173	3.962	0.047	0.708	0.505–0.995	0.072	88	110.321
Admission[a]									
MAQ	–0.671	0.274	6.010	0.014	0.511	0.299–0.874	0.213	93	58.015
DAI	–0.292	0.136	4.584	0.032	0.747	0.572–0.976	0.241	92	56.509
CRS	–0.739	0.277	7.101	0.008	0.477	0.277–0.822	0.293	88	53.660

[a]Logistic regression. Dependent variable is relapse, or admission (yes/no); covariates are: negative symptoms (BPRS neg), symptom relabeling and hypothetical contradiction (SAIf1), illness awareness (SAIf2), depot medication (yes/no).
[b]Analyses performed on 83 patients who had a rating on each adherence instrument.
Note: SE, standard error; CI, confidence interval.

patients were admitted to a psychiatric hospital. The average monthly admission rate in our sample was 1.2%. Each quarter between three and five patients were admitted. Two patients (13%) were admitted twice and one patient (6%) had three separate admissions. Most admitted patients (81%) were admitted once.

Logistic regression analysis shows that the risk for relapse decreases with increasing adherence rates. This relation was found for all three adherence measures but was only significant for the MAQ (see Table 2). Besides a slight increase in risk of relapse, time to relapse is shorter for patients with lower adherence rates. Again this was only significant for the MAQ (see Table 3). For both analyses the explained variation ranges from 0.05 to 0.09, which in terms of Cohen's effect size criteria for R^2, is an indication for a low to medium effect (Cohen, 1988).

The risk for admission also decreases with increasing adherence rates. Although this relation was found for all

Table 3 Prediction of time to relapse and admission

	β	SE	Wald	Sig.	Exp(β)	95% CI lower	95% CI upper	R_p[b]	*N*
Relapse[a]									
MAQ	–0.378	0.124	9.256	*0.002*	0.685	0.537	0.874	0.068	93
DAI	–0.096	0.066	2.121	0.145	0.908	0.798	1.034	0.052	92
CRS	–0.219	0.101	4.683	0.030	0.803	0.659	0.980	0.048	88
Admission[a]									
MAQ	–0.433	0.195	4.936	0.026	0.649	0.443	0.950	0.101	93
DAI	–0.228	0.110	4.339	0.037	0.796	0.642	0.987	0.120	92
CRS	–0.463	0.150	9.475	*0.002*	0.630	0.469	0.845	0.144	88

[a]Cox Regression; covariates are: negative symptoms (BPRS neg), symptom relabeling and hypothetical contradiction (SAIf1), illness awareness (SAIf2), depot medication (yes/no). Hazard rates were proportional.
[b]Explained variation (R_p) (Hosmer and Lemeshow, Applied Survival Analysis. Regression Modeling of Time to Event Data).
Analyses performed on 83 patients who had a rating on each adherence instrument.
Note: SE, standard error; CI, confidence interval.

Table 4 Sensitivity and specificity for relapse and admission ($N = 119$)

	Relapse		Admission	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
MAQ	63.6	59.7	87.5	54.5
DAI	18.2	90.0	20.0	87.0
CRS	34.0	90.3	38.5	81.8

three adherence instruments, it was only significant for the MAQ and CRS (see Table 2). Time to admission is shorter for non-adherent patients but this was only significant for the CRS (see Table 3). Explained variation for chance of, and time to admission ranges from 0.10 to 0.29, which in terms of Cohen's effect size criteria for R^2, an indication for a medium to strong effect (Cohen, 1988).

Table 4 shows the sensitivity and specificity of the three instruments to detect non-adherence. Both the DAI and CRS label most patients as adherent (respectively 86% and 79%) and therefore sensitivity is low while specificity is high. Compared to the DAI and CRS, the MAQ has better sensitivity and specificity.

Discussion

In our previous study (Kikkert *et al.*, 2008) we concluded that concurrent validity of the MAQ, DAI and CRS was low. However this did not rule out the possibility that one of them is a good index of medication adherence. To explore this possibility, we evaluated the predictive validity of these three measures in this study.

There is significant evidence for the efficacy of antipsychotic medication. Therefore, in a sample of responsive stabilized outpatients, it seems reasonable to assume a relationship between medication intake behaviour and clinical outcome. In this study we found that the MAQ was predictive for relapse and for time to relapse. The MAQ and CRS were both predictive for hospital admission. The CRS was also predictive for time to hospital admission. The clinical relevance of these effects is however limited. Adherence rates on any of the three measures could only explain a relatively small proportion of the variation. Although non-adherent patients in general had higher relapse and admission rates, sensitivity shows that out of all patients who relapsed or got admitted, the proportion labelled as non-adherent was very low. Although sensitivity and specificity of the MAQ was better, 42% of patients who were non-adherent according to the MAQ still did not relapse, and 35% of adherent patients did relapse.

Out of the two self-report instruments, the DAI had the worst predictive validity. The DAI focuses on patient's attitudes towards medication whereas the MAQ items directly relate to medication intake behaviour. The latter seemed to be a slight better approach in measuring adherence, although Karow *et al.* (2007) found that subjective well-being may also be useful in predicting adherence.

Other studies demonstrated that clinician ratings of adherence have poor validity (Byerly *et al.*, 2005; Byerly *et al.*, 2007; Remington *et al.*, 2007). Our results confirm this finding. Clinicians performed relatively better at estimating adherence behaviour of patients with poorer outcome defined as admission to hospital. In addition to more severe symptoms, patients who get admitted often have less social support and live alone. These are also associated with non-adherence (Fenton *et al.*, 1997; Pinikahana *et al.*, 2002; Perkins, 2002) which may help explain why patients with high risk profiles for non-adherence are more easily detected by clinicians. Therefore, treating physicians to base their impression of adherence on clinical state (symptomatology, clinical global impression) it is possible that physician-rated adherence would have a stronger relationship with clinical state.

This study, however, also has its limitations. In a cohort study, Valenstein *et al.* (2002) examined adherence behaviour in two consecutive years and found that 83% of adherent patients, and 70% of non-adherent patients remained respectively adherent and non adherent the following year. This may indicate that adherence is relatively stable for the majority of patients over two consecutive years. Nevertheless, in our study we only measured adherence at baseline and are unaware of any changes later in time. Patients may have changed their adherence behaviour after the baseline measurement. Patients who suffered mild or no symptoms may be more tempted to stop using their medication. However, patients who experienced exacerbation of symptoms due to non-adherence may have avoided relapse or hospitalization by increasing their medication intake in time. To reduce the influence of possible changes in adherence behaviour in time, we repeated our logistic regression analysis focussing only on relapses that occurred within the first three, and six months. This did not change our results, none of the instruments were predictive for relapse in the first three or six months.

If a clinician was not sure about the patients condition over a certain period of time, the information on the clinical course rating was left blank. Nevertheless, the validity of the clinical course rating is not known and information regarding psychotic relapse can be affected by misinterpretation. This is not the case for admission data, which are therefore less likely to be inaccurate.

It is possible that a psychosis was induced by other causes such as life events or drug abuse. Although this would have strengthened our design, this information was not available for our sample. We do know from other studies that the increased risk for psychosis in drug abusers is at least partly due to non-adherence (Perkins *et al.*, 2008; Ascher-Svanum *et al.*, 2006).

Relapse could also have been caused if inadequate doses of antipsychotic medication were prescribed. In our analysis, the daily dosage, expressed as the proportion of the defined daily doses of antipsychotic medication (WHO, 2003), turned out to have no influence on chance of, or time to relapse or admission. Therefore we conclude that patients in our sample received appropriate doses of medication.

Up to date subjective self-report tests are the most frequently used methods to measure adherence. Although there are a wide variety of measures available, most of them are similar to either the MAQ, DAI or CRS. In a previous paper (Kikkert *et al.*, 2008) we demonstrated that the MAQ, CRS and DAI do not measure the same trait. In this article we were able to determine the predictive validity in a European sample of treated stabilized outpatients with schizophrenia based on two significant clinical outcomes; relapse and admission. We found that none of the three instruments were able to clearly distinguish patients who are likely to relapse or get admitted to hospital in the following 12 months. Given the results of this study and our previous study (Kikkert *et al.*, 2008) we conclude that the MAQ, CRS and DAI do not validly measure adherence and their use for scientific purposes is questionable. Unfortunately, the majority of adherence studies in patients with schizophrenia use these, or similar type of instruments. Researchers should be aware of the poor validity of subjective instruments and the impact it may have on study results. Given the convenience of subjective instruments, researchers should continue to strive for the development of valid, and easy to use adherence measures. Until these are available, objective instruments such as electronic medication monitoring, pill count or pharmacy based measures may be more preferable.

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Declaration of interest statement

The authors have no competing interests.

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