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REVIEW ARTICLE

How often do patients with psychosis fail to adhere to treatment programmes? A systematic review

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ABSTRACT

Background. Studies that assess the rates of psychotic patients who fail to adhere to treatment programmes have generated heterogeneous results, with estimates ranging from 24 to 90%. This paper presents findings from a systematic review on adherence to treatment by patients with psychosis. Its purpose is to provide an overall estimate of treatment non-adherence in community psychiatric services, and to analyse and study patient characteristics explaining the between-study heterogeneity in rates of non-adherence.

Method. A systematic review of published studies that report rates of non-adherence with medication and scheduled appointments by psychotic patients in community settings has been undertaken.

Results. A total of 103 studies were included in this systematic review. Eighty-six of these studies were suitable for data re-analysis. The overall weighted mean rate of non-adherence, calculated in a sample of 23 796 patients, was 25·78%. A linear regression analysis of non-adherence rates on background characteristics showed that sample size was negatively associated with non-adherence rates, while first-contact cases and low-adherence cases, in comparison with ongoing cases, were associated with higher non-adherence rates. Factors associated with poor compliance included: lack of insight; positive symptoms; younger age; male gender; history of substance abuse; unemployment; and low social functioning.

Conclusions. Approximately one in four patients with psychosis fails to adhere with treatment programmes. Preventive evidence-based clinical interventions should be routinely implemented in community settings to reduce patient non-adherence.

INTRODUCTION

The concept of adherence to treatment programmes, previously defined 'compliance', has been described as 'the extent to which a person's behaviour coincides with the medical advice given' (Sackett & Haynes, 1976). A definition of non-adherence therefore includes: the failure to enter a treatment programme, premature termination of therapy and incomplete implementation of instructions, including prescriptions. Treatment non-adherence has a major impact on the effectiveness of therapeutic interventions and presents many problems in clinical practice (Haynes *et al.* 2002).

Treatment non-adherence is a common problem in psychiatry. In recent years many studies have been conducted in a wide range of settings and contexts of psychiatric care to estimate rates of non-adherence to medication and/or scheduled appointments, as well as to identify variables associated with premature discontinuation of contacts. According to these studies, treatment non-adherence can be classified into

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adherence to medication and adherence to scheduled appointments. Cramer & Rosenheck (1998) found that in patients with psychiatric disorders adherence is lower than among patients with physical disorders. Their study showed that, depending on the design adopted and the number of patients evaluated, non-adherence rates in psychiatry ranged from 24 to 90%, with a mean level on non-adherence of around 60%. However, only adherence to medication was investigated; moreover, the majority of included studies were published before 1980 and results might not fully apply to the current organization of community-based psychiatric services.

In patients with psychosis, compared with patients suffering from other mental disorders, non-adherence may have wider clinical implications, since psychotic disorders require long-term treatment and regular out-patient contacts to decrease the likelihood of relapse and recurrences. Poor compliance with antipsychotic medication, for example, is associated with increased hospital admissions and poorer outcomes (Gray *et al.* 2002), and also with problems in the management of first-episode schizophrenic patients (Robinson *et al.* 1999; McGorry & Killackey, 2002). Kampman & Lehtinen (1999) reviewed the literature on factors associated with non-compliance in psychosis and observed that unpleasant side-effects of medication, attitude towards medication, delusional symptoms, substance abuse, insight and supportive family environment had the strongest correlation with compliance. Fenton and colleagues (1997) suggested that compliance is a multi-determined phenomenon with many different factors associated with it.

Although the majority of studies have concentrated on psychotropic medication, a number of studies have assessed the rate on non-adherence to scheduled appointments. These studies have received little attention and have never been systematically reviewed (Centorrino *et al.* 2001). The present systematic review was therefore carried out to answer the following research questions: (1) how often do patients with psychosis fail to adhere with treatment programmes?; (2) do studies estimating adherence to medication generate different non-adherence rates in comparison to studies estimating non-adherence to scheduled appointments?; (3) are there study and/or patient characteristics which can explain the between-study variability in rates of non-adherence?; (4) what are the most common factors related to non-adherence?

METHOD

Inclusion criteria

All articles reporting rates of treatment non-adherence were considered for inclusion if they included patients with schizophrenia, psychoses or severe mental disorders. Studies were included if adherence was the primary outcome measure and if patients were recruited in a psychiatric setting (studies conducted in medical wards of general hospitals or in emergency rooms were excluded). Studies on compulsory treatment and those assessing adherence to initial psychiatric appointments were excluded. However, studies focusing on rates of adherence with aftercare programmes (i.e. appointments after hospital discharge) were included. Only studies published from 1980 onwards were included.

Search strategy

Relevant studies were located by searching *Medline* and *PsychINFO* from January 1980 onwards. The following keywords were used: 'adherence' or 'compliance' or 'dropout' or 'attendance' or 'concordance' or 'termination' or 'continuity' and 'schizophrenia' or 'psychosis' or 'severe mental disorders'. Reference lists of relevant papers and previous systematic reviews were hand searched for published reports and citations of unpublished research.

Data extraction

An *ad hoc* data extraction form was developed. From each included study two reviewers independently extracted the following information: country of publication, study setting, design, length of follow-up, sample size, patient characteristics, definition of non-adherence, proportion of non-adherent subjects and factors associated with non-adherence. Definitions of non-adherence were grouped into two categories: (1) not taking psychotropic drugs as prescribed; (2) not keeping appointments as scheduled. Several methods have been reported to establish adherence; these were grouped into four categories: (1) patient's interview; (2) case note

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evaluation/physician interview; (3) rating scale; (4) urine test.

Statistical analysis

Non-adherence rates were calculated by dividing the number of patients meeting each study's definition of non-adherence out of the total number of enrolled patients. Data are presented as weighted mean rates per 100 together with the 95% confidence interval (CI) (Bland & Kerry, 1998). When only percentages were reported, they were converted into absolute numbers. In the case of disagreement between the two reviewers, data were not retained. Linear regression analysis was run to assess the association between adherence rates and the following independent variables: definition of adherence (dichotomous variable: scheduled appointments = 0, medication = 1), study design (categorical variable: cross-sectional, 0–6 months of follow-up, 7–12 months of follow-up, >12 months of follow-up), setting (dichotomous variable: other = 0, out-patients = 1), sample size (continuous variable), diagnosis (dichotomous variable: other = 0, schizophrenia = 1), patients' characteristics (categorical variable: patients already in treatment, first-contact patients, low-adherence patients). A non-parametric bootstrap method of statistical accuracy was employed (Efron & Tibshirani, 1986). All analysis was conducted using STATA 7.0 (StataCorp, 2001).

Table 1. *Characteristics of included studies*

	Studies *N*	%
Country		
Europe	35	33·98
USA	48	46·60
Other	20	19·42
Definition of adherence		
Not keeping appointments as scheduled	54	52·43
Not taking drugs as prescribed	49	47·57
Design		
Prospective	71	68·93
Cross-sectional	32	31·07
Length of follow-up		
0–6 months	29	41·43
7–12 months	20	28·57
⩾12 months	12	17·14
Related to definition	9	12·86
Setting		
In-patients	17	16·50
Out-patients	61	59·22
Hospital discharge patients	25	24·27
Sample size		
<50	21	21·43
51–100	27	27·55
101–150	15	15·31
>151	35	35·71
Diagnosis		
Schizophrenia	36	34·95
Psychosis	30	29·13
Severe mental disorder	37	35·92
Patient characteristics		
First-contact	14	13·59
Already in treatment	86	83·50
History of low adherence	3	2·91
Methods to assess adherence		
Patient interview	9	8·74
Case note/physician interview	78	76·70
Rating scales	14	13·59
Urine markers	1	0·97

RESULTS

Characteristics of included studies

The search yielded 288 citations of potentially relevant studies. Of these, 103 studies met the inclusion criteria and were considered in this systematic review (see Appendix). Data suitable for re-analysis were reported in 86 studies. Seventeen studies were excluded because they did not report either the number of enrolled patients or the number of non-adherent patients at follow-up. Table 1 shows that the majority of the included studies was conducted in USA. Slightly more than 50% assessed adherence to scheduled appointments, while the remaining studies assessed adherence to prescribed medication. The majority of the studies adopted a prospective design, with a follow-up ranging from 0·5 to 48 months (median 7·5 months, mean 11·2 months, S.D. 10·6). This median length of follow-up, however, was calculated excluding studies assessing non-adherence with aftercare programmes, since the length of follow-up in these reports varied for each included patient depending on the length of time between hospital discharge and the scheduled appointment (the follow-up of these studies was defined 'related to definition'). The mean number of patients per study was 253·8 (S.D. 440·4, median 103, range 20–2257). More than one-third of the studies included only patients with schizophrenia, while the remaining two-thirds included patients with psychosis and with severe mental disorders (including schizophrenia, but not separately specified). In the majority of the studies, patients were already receiving treatment.

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Table 2. *Subgroup analyses of studies assessing rates of non adherence*

	Patients *N* (Studies)	Unweighted rate per 100	Weighted rate per 100 (95% CI)
Country			
Europe	4137 (32)	38·40	34·32 (28·52, 40·13)
USA	12 292 (38)	35·81	24·37 (20·12, 28·62)
Other	7367 (16)	41·14	23·35 (13·74, 32·95)
Definition of adherence			
Not keeping appointments as scheduled	17 314 (47)	33·66	24·30 (20·65, 27·96)
Not taking drugs as prescribed	6482 (39)	42·70	29·74 (22·81, 36·67)
Design			
Prospective	17 869 (63)	35·34	25·40 (21·53, 29·27)
Cross-sectional	5927 (23)	44·39	26·94 (19·93, 33·95)
Length of follow-up			
0–6 months	6204 (26)	35·50	29·64 (23·16, 36·12)
7–12 months	4537 (16)	37·54	27·40 (19·74, 35·05)
⩾12 months	5913 (12)	33·01	17·60 (8·64, 26·57)
Related to definition	1215 (9)	34·09	34·24 (27·86, 40·62)
Setting			
In-patients	2345 (15)	41·31	25·97 (15·87, 36·07)
Out-patients	13 887 (47)	38·86	28·41 (23·93, 32·90)
Hospital discharge patients	7564 (23)	33·15	20·90 (14·87, 26·93)
Sample size			
<50	638 (17)	48·47	48·75 (39·93, 57·56)
51–100	1664 (22)	39·64	39·12 (31·82, 46·42)
101–150	1614 (13)	39·59	39·53 (31·33, 47·72)
>151	19 880 (34)	30·50	22·82 (18·01, 27·62)
Diagnosis			
Schizophrenia	5790 (30)	40·64	25·04 (17·42, 32·66)
Psychosis	6372 (24)	37·48	26·41 (19·74, 33·08)
Severe mental disorders	11 634 (32)	35·28	25·81 (21·26, 30·36)
Patient characteristics			
First-contact	1735 (13)	44·62	46·92 (38·70, 55·13)
Already in treatment	21 389 (70)	36·86	23·21 (20·02, 26·39)
History of low adherence	672 (3)	52·40	53·27 (5·67, 100·88)

Overall rate of non-adherence

The overall weighted mean rate of non-adherence, calculated in a sample of 23 796 patients (86 studies), was 25·78% (CI 22·46, 29·10). Excluding five studies where absolute numbers were inferred from percentages reported in the text, the overall weighted mean rate of non-adherence, calculated in a sample of 21 646 patients (81 studies), was 27·00% (CI 23·59, 30·41).

Subgroup analysis

A subgroup analysis was carried out by stratifying the 86 studies by the characteristics reported in Table 2. Non-adherence rates were non-significantly higher in studies conducted in Europe compared with those conducted in the USA. Studies assessing non-adherence to medication obtained slightly higher rates in comparison with studies assessing non-adherence to scheduled appointments, but this difference was not significant, as can be seen from the overlapping confidence intervals. Rates of non-adherence non-significantly decreased with the increasing follow-up and significantly decreased with the increasing sample size, from 48·75% (CI 39·93, 57·56) in studies with <50 patients to 22·82 (18·01, 27·62) in studies with >150 patients. No difference emerged with respect to diagnosis, while studies enrolling first-contact cases, or patients with a history of low-adherence, provided significantly higher non-adherence rates than studies conducted in patients already receiving treatment (Table 2).

Determinants of non-adherence rates

To assess the importance of the characteristics of the 86 studies, both in terms of study design

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Table 3. *Determinants of non-adherence rates: linear regression analysis*†

Explanatory variable	Coefficient	S.E.	Bias corrected 95% CI
Definition of adherence (appointments = 0, medicines = 1)	4·425	4·583	−4·055, 13·794
Study design			
Cross-sectional	Ref.		
Prospective/0–6 months	−7·506	5·714	−19·099, 3·535
Prospective/7–12 months	−7·214	5·983	−18·613, 5·187
Prospective/⩾13 months	−8·936	6·306	−21·503, 3·030
Prospective/not applicable	−6·792	6·538	−20·484, 5·390
Setting (other = 0, out-patients = 1)	2·914	3·702	−4·419, 10·131
Sample size (continuous variable)	−5·443	1·557	−8·394, −2·259*
Diagnosis (other = 0, schizophrenia = 1)	3·765	4·556	−4·624, 13·371
Patients' characteristics			
Already in treatment	Ref.		
First-contact	14·087	5·859	2·545, 25·613*
History of low-adherence	27·343	11·967	0, 51·226*
Constant term	44·694	6·247	31·258, 55·958

† Linear regression analysis, bootstrapped 95% CIs, 5000 repetitions. Number of observations included into the model = 86; $R^2 = 32{\cdot}2\%$; Adjusted $R^2 = 23{\cdot}2\%$. Positive coefficients indicate that explanatory variables included into the model were correlated with higher non-adherence rates; positive upper and lower limits of confidence intervals indicate a statistically significant positive association. Negative coefficients indicate that explanatory variables included into the model were correlated with lower non-adherence rates; negative upper and lower limits of confidence intervals indicate a statistically significant negative association.

Ref., Reference category.

* $P < 0{\cdot}05$.

and patient characteristics, on non-adherence rates, a bootstrapped linear regression analysis was conducted (Table 3). Only two independent variables were significantly associated with non-adherence, namely sample size and patients' characteristics. Sample size was negatively associated with non-adherence rates, while first-contact cases and patients with a history of low-adherence, in comparison with patients already in treatment, were associated with higher non-adherence rates.

Patients' characteristics associated with adherence and non-adherence

Table 4 presents the factors influencing adherence. In 13 of the studies insight was found to be associated with adherence, and lack of insight was found to be associated with non-adherence in 14 studies. Psychopathology interfered with patients' adherence in 15 studies, although six studies found psychotic symptoms associated with adherence. Previous psychiatric contacts were associated with adherence in eight studies, while a history of non-adherence was found to be predictive of future non-adherence in 11 studies (Table 4). Living alone, high education and good social functioning were associated with adherence. In contrast, being young, male, having history of substance abuse, unemployment and low social functioning were associated with non-adherence.

DISCUSSION

Study limitations

This study has two main limitations. First, studies published before 1980 were not included. This review exclusion criteria was motivated by the fact that most studies conducted before 1980 recruited patients in psychiatric hospitals or in in-patient settings, or assessed adherence to out-patient programmes implemented in a hospital-based context of care where community facilities were lacking (Cramer & Rosenheck, 1998). In contrast, since 1980 many European and non-European countries developed community-oriented systems of psychiatric care, with a diminished emphasis on psychiatric hospitals and a high priority given to out-patient care

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Table 4. *Factors associated with adherence and non-adherence*

	Studies *N*	%
Factors related to adherence		
Insight	13	12·62
Previous psychiatric contacts	8	7·76
Family support	7	6·80
Psychotic symptoms	6	5·82
Better social functioning	5	4·85
Living alone/being single	5	4·85
Higher education	4	3·88
Good therapeutic alliance	4	3·88
Facilities for appointments	4	3·88
Factors related to non-adherence		
More psychopathology	15	14·56
Lack of insight	14	13·59
Non-adherence in the past	11	10·68
Young age	9	7·76
Substance abuse	8	7·76
Unemployment	8	7·76
Affective features	6	5·82
Long hospital stay	6	5·82
Being married	6	5·82
Male sex	5	4·85
Low social functioning	4	3·88
Cognitive impairment	4	3·88
Lack of family support	4	3·88
Employment	4	3·88

delivered by community mental health centres (Mosher & Burti, 1994).

A second limitation is that the quality of the studies was not assessed. For example, we adopted no *a priori* exclusion criteria based on sample size, length of studies or diagnostic criteria. However, the subgroup and regression analysis investigated whether sample size, duration of follow-up, definition of adherence and other study characteristics were associated with the resulting proportion of non-adherent patients. In contrast, the way in which adherence was assessed was not studied, because this was very unreliable information. In fact, the majority of included studies did not explicitly state how adherence was measured; presumably, investigators asked patients or physicians directly, and only in a minority of cases rating scales or direct methods, such as urine tests, were adopted. The regression analysis explained 32% of the total variance. Although this suggests that the model contains some explicatory independent predictors of non-adherence, the majority of variance remains unexplained. It is therefore likely that other independent variables might have contributed to some between-study heterogeneity.

Clinical implications

In community psychiatric settings, treatment non-adherence remains a crucial problem that can result in long-term therapeutic plans being ineffective (Angermeyer & Katschnig, 1997; Breen & Thornhill, 1998; Lindstrom & Bingefors, 2000; Angermeyer & Schulze, 2001). Considering the whole sample of studies included in the present systematic review, around one in four patients with psychosis failed to adhere with treatment programmes. This finding was lower than figures quoted in other studies (Fenton *et al*. 1997; Cramer & Rosenheck, 1998; Kampaman & Lehtine, 1999; Oehl *et al*. 2000; Lacro *et al*. 2002). Lacro and colleagues (2002), who investigated medication non-adherence in patients with schizophrenia, adopted narrow inclusion criteria and found a mean rate of non-adherence of 41·2%. Adopting a stricter set of inclusion criteria, corresponding to only five study reports, they found a mean rate of non-adherence of 49·5%. It is likely, therefore, that the mean rate of non-adherence calculated in the present study should be considered bearing in mind the different criteria adopted, which led to the inclusion of heterogeneous samples of subjects with schizophrenia, psychosis or severe mental disorders. These criteria, in addition to studies investigating medication adherence, allowed the inclusion of studies investigating adherence to scheduled appointments. This approach was followed to produce findings relevant to everyday clinical practice, where narrowly defined patients and strict outcome definitions are not applicable.

A second interesting finding is that the rates of non-adherence by patients to prescribed medication were only slightly higher than those to scheduled appointments, with wide and overlapping confidence intervals. A possible explanation for this might relate to the difficulty of making a clear distinction between these two categories. Patients who do not want to take the prescribed medication might miss the scheduled appointments, or, vice versa, patients who want to discontinue the contact with the community psychiatric service might also stop taking the prescribed medication. However, using each study's definition of non-adherence, overall rates were similar, thus strongly supporting the relevance of not ignoring adherence to

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appointments in favour of medication adherence, especially in outcome studies carried out in everyday clinical conditions.

The regression of non-adherence rates on background study and patient characteristics demonstrated that sample size and patients' characteristics were determinants of non-adherence rates. Studies recruiting first-contact patients and studies recruiting patients with a history of non-adherence were associated with higher non-adherence rates. Although this finding may seem somewhat circular – with patients identified as having low-adherence providing to have high rates of non-adherence – it is nevertheless a frequently reported finding in primary studies. The characteristics of study patients have often been described as the most important factors associated with adherence. Moreover, adherence has been found to be a dynamic process that is likely to change over time and varies substantially from patient to patient (Perkins, 1999). Sample size was negatively associated with non-adherence rates, meaning that studies with large samples provided lower rates than studies with small samples of patients. This might have occurred because of less sensitivity in detecting non-adherence in larger studies. Alternatively, studies with small samples might have suffered from selection bias (Skapinakis & Lewis, 2001), that is, they might have recruited selected samples of low-adherence subjects. Berghofer and colleagues (2002), who carried out a study on the prevalence of treatment discontinuity in out-patients, noted that the relatively low inclusion rate of patients from the three catchment areas selected for the recruitment may have influenced the representativeness of the study, thus over emphasizing the estimate of non-adherence. In contrast, studies enrolling large sample of patients are more likely to generate cohorts of typical subjects who are representative of the whole populations of everyday patients. This was the case, for example, in studies using case registers, which identified all patients meeting some pre-defined conditions in a given period of time (Sytema *et al.* 1997).

Factors associated with non-adherence

It was a complex procedure to extract from each study a list of variables associated with non-adherence. Each study considered its own set of potential predictors, in some cases identified using adherence as the dependent variable and in others using non-adherence as the dependent variable. Although some contrasting data inevitably emerged, some variables, which were repeatedly found to be predictors of non-adherence, allowed a set of typical characteristics of non-adherent subjects to be delineated. Young male patients with poor insight of illness, a history of substance abuse, unemployed and with low social functioning emerged as those at higher risk of failing to adhere with treatment programmes. The presence of these characteristics, therefore, should be routinely reviewed in clinical practice in order to make a judgement regarding the likelihood of non-adherence with treatment plans.

Conclusions

Effective interventions, backed by scientific evidence, can be implemented by community psychiatric services for reducing patient non-adherence. Chen (1991), who conducted a narrative review of clinical interventions in psychoses, recommended the scheduling of appointments before release from in-patient treatment, the use prompts in the forms of letters and telephone calls to encourage patients to keep their appointments and the offer education about treatment and medication. Zygmunt and colleagues (2002) suggested that models of community care such as assertive community treatment and interventions based on principles of motivational interviewing are promising tools for reducing non-adherence rates. Clinicians should, therefore, be aware that once the reasons for non-compliance have been ascertained, there may be many possible solutions available to encourage adherence to treatment (Nosé *et al.* 2003), both in terms of adherence to medication and appointments.

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APPENDIX: STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Adams, J. & Scott, J. (2000). Predicting medication adherence in severe mental disorders. *Acta Psychiatrica Scandinavica* **101**, 119–124.

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