

Clinical interventions for treatment non-adherence in psychosis: meta-analysis

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Background Studies investigating the efficacy of clinical interventions for reducing treatment non-adherence have generated contrasting findings, and treatment non-adherence remains common in clinical practice.

Aims To systematically review whether there are effective clinical interventions that community psychiatric services can implement to reduce non-adherence.

Method Systematic review and meta-regression analysis of randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were used to assess the efficacy of interventions to enhance adherence.

Results We reviewed 24 studies, more than half of which were RCTs. In 14 studies the experimental intervention was an educational programme. Five studies evaluated pre-discharge educational sessions, three studies explored the benefit of psychotherapeutic interventions and two studies looked at the effect of telephone prompts. The overall estimate of the efficacy of these interventions produced an odds ratio of 2.59 (95% CI 2.21–3.03) for dichotomous outcomes, and a standardised mean difference of 0.36 (95% CI 0.06–0.66) for continuous outcomes.

Conclusions Community psychiatric services can potentially use effective clinical interventions, backed by scientific evidence, for reducing patient non-adherence.

Declaration of interest None.

Treatment non-adherence remains one of the greatest challenges in psychiatry. It has been estimated that 20–50% of any patient population is at least partially non-compliant, and that in patients with schizophrenia and related psychotic disorders rates can run as high as 70–80% (Breen & Thornhill, 1998). Adherence has been defined as the extent to which a person's behaviour coincides with the medical advice given (Sackett & Haynes, 1976). The definition of non-adherence includes failure to enter a treatment programme, premature termination of therapy and incomplete implementation of instructions (including prescriptions).

Several randomised controlled trials (RCTs) and controlled clinical trials (CCTs) have been conducted to assess the efficacy of a wide range of clinical interventions to reduce non-adherence in patients with psychosis (Chen, 1991). The focus of most of these studies has been the reduction of non-adherence to psychotropic medication or to scheduled appointments. Zygmunt and colleagues, who systematically reviewed RCTs and CCTs assessing psychosocial interventions for improving medication adherence in schizophrenia, showed that only a third of included studies reported significant treatment effects (Zygmunt *et al*, 2002). However, this review did not employ meta-analytic techniques, excluded studies assessing interventions for improving adherence to scheduled appointments and included highly selected populations of patients with schizophrenia. In this systematic review we adopted meta-analytic techniques to establish whether there are effective clinical interventions that community psychiatric services can implement to reduce medication and appointment non-adherence in patients with psychosis.

METHOD

Inclusion criteria

The review included studies assessing the efficacy of interventions aimed at reducing

patient non-adherence. Studies with a random assignment design and studies with a comparison of outcome between two or more groups without a random assignment design were considered for inclusion. Only studies of patients with schizophrenia and related disorders or psychoses were selected. Studies, written in English, were included if adherence was one of the primary outcome measures, if patients were recruited in a psychiatric setting and if the control group received standard care. Studies of compulsory treatment and those assessing adherence to initial appointments were excluded. However, studies focusing on adherence to after-care programmes (i.e. appointments after hospital discharge) were included.

Search strategy

Relevant studies were located by searching Medline and PsycINFO 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. 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. Two reviewers independently extracted the following information: country in which the study was conducted, study setting, design, length of follow-up, main patient characteristics, description of experimental and control intervention, and definition of non-adherence. Definitions were grouped into two categories:

- (a) not taking psychotropic drugs as prescribed
- (b) not keeping appointments as scheduled.

Several methods have been reported to establish adherence; these were grouped into four categories:

- (a) patient interview
- (b) case-note evaluation
- (c) rating scale
- (d) urine test.

Clinical interventions for improving patient adherence were grouped into the following categories:

- (a) educational strategies

- (b) psychotherapy
- (c) prompts
- (d) specific service policies
- (e) family interventions.

From each study the number of patients assigned to the experimental and control group was extracted, as was the number of patients meeting each study's definition of non-adherence. When appropriate, if only percentages were reported, they were converted into absolute numbers. For continuous outcomes the mean scores on any rating scale assessing non-adherence and the number of patients included in this analysis were recorded. Mean scores were recorded with the standard deviation (s.d.) or standard error (s.e.) of these values. When only the s.e. was reported, it was converted into s.d. using the method described by Altman & Bland (1996).

Statistical analysis

Dichotomous outcomes were summarised by calculating a Peto odds ratio (OR) for each study, together with the 95% confidence interval (CI). An overall weighted OR was then calculated as a summary measure. Continuous outcomes were analysed by calculating a standardised mean difference (SMD) for each study. This measure gives the effect size of an intervention in units of standard deviation so that scores from different outcome scales can be combined into an overall estimate of effect. A random effects model, which takes into consideration any between-study variation, was adopted to combine the effect sizes. Heterogeneity of treatment effect between studies was formally tested using the χ^2 statistic. A meta-regression technique was in addition adopted to examine the extent to which study-level covariates predicted treatment effect.

RESULTS

The search

The electronic search generated 47 studies that met the inclusion criteria. In 23 of these (Appendix 1) results were reported without absolute numbers suitable for re-analysis. The remaining 24 studies (Appendix 2), which reported outcome data suitable for re-analysis, were included in our systematic review. Excluded and included studies did not differ with respect to the proportion of positive studies: a claim of efficacy was present in 13 out of

23 excluded studies (57%, 95% CI 34.4–76.8) and in 15 out of 24 included studies (63%, 95% CI 40.5–81.1) ($\chi^2=0.174$, $P=0.676$).

Characteristics of included studies

The majority of included studies were conducted in North America, four in Europe, four in China and one in Egypt (Table 1). A random allocation design was adopted in 58% of studies, whereas the others adopted a CCT design. The length of follow-up ranged from 2 weeks to 72 weeks, with a median of 24 weeks; this figure, however, did not include studies assessing non-adherence to after-care 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 (Table 1). The mean number of patients per study was 149 (s.d. 159.3, median 81.5, range 21–660). Most studies were performed in out-patient settings, 38% followed patients from hospital to community and only a minority were conducted in hospital.

In 14 studies the experimental intervention was an educational programme, in five cases specifically developed for family members. Five studies evaluated specific service policies, such as pre-discharge contacts between patients and the community team, or pre-discharge educational sessions about antipsychotic medication. Three studies assessed the benefit of psychotherapeutic interventions, in two cases adopting a cognitive approach and in one case a psychodynamic approach. Two studies assessed the effect of prompts in the form of telephone calls. Usual care was the control intervention in 63% of studies; in the others a non-specific intervention, similar to the experimental programme in terms of number of sessions, was employed. These interventions were developed to reduce non-adherence to psychotropic medication in 14 studies, assess attendance at first appointments after hospital discharge in six studies and increase attendance at scheduled appointments in four studies (Table 1).

Outcome of studies

Of the 24 included studies, 19 reported dichotomous and 5 continuous outcome data. In 4 studies dichotomous outcome data were inferred from percentages reported in the study tables. The treatment

effect of each study is presented in Figs 1 and 2. Overall, clinical interventions for reducing patient non-adherence were significantly more effective than control interventions. The pooled OR for dichotomous outcomes was 2.59 (95% CI 2.21–3.03; Fig. 1); similarly, the pooled SMD for continuous outcomes was 0.36 (95% CI 0.06–0.66; Fig. 2). The funnel plot for studies with dichotomous outcome was not symmetrical, indicating that publication bias could not be ruled out (Fig. 3).

Subgroup analysis

A subgroup analysis was carried out by stratifying the 19 studies with dichotomous outcome data by the study characteristics reported in Table 2. Studies adopting an RCT design yielded an OR similar to studies adopting a CCT design. The effect of clinical interventions for reducing non-adherence was greater in studies with a short follow-up period (OR 2.27, 95% CI 1.78–2.90) than in those with a follow-up of 6 months or more (OR 1.70, 95% CI 1.04–2.78); moreover, it was slightly greater in studies enrolling homogeneous populations of patients with schizophrenia, and in studies assessing adherence with hospital discharge programmes (Table 2). Studies assessing adherence to medication yielded a slightly higher OR than studies assessing adherence to out-patient and post-discharge appointments. All five categories of clinical interventions were more effective than control interventions in reducing patient non-adherence.

Meta-regression analysis

The individual contribution of each of the above-mentioned study characteristics to treatment outcome was assessed by a meta-regression analysis (Table 3). Only two covariates were significantly associated with treatment outcome, namely length of follow-up and diagnosis. Length of follow-up was significantly associated with a less favourable treatment outcome, whereas diagnosis of schizophrenia was associated with a more favourable treatment effect.

DISCUSSION

Interpretation of the results in the context of previous reviews

This systematic review showed that community psychiatric services can provide effective clinical interventions, backed by

Table 1 Characteristics of included studies

Study	Country	Design	Duration (months)	Setting	Special population of patients	Sample size (n)		Description of experimental intervention	Description of control intervention	Study end-point	Method used to assess non-adherence
						Experimental group	Control group				
Boswell <i>et al</i> (1983)	USA	RCT	12	Out-patients	No	184	185	Telephone call before scheduled appointments	Usual care	Not keeping appointments as scheduled	Case notes
Chaplin & Kent (1998)	UK	RCT	24	Out-patients	No	28	28	Educational sessions about medication	Usual care	Missing more than 2 weeks of medication	Patient interview
Cramer & Rosenheck (1999)	USA	RCT	24	Out-patients	Low-adherence patients	41	40	Educational sessions to remember daily medication	Usual care	Not taking medication as prescribed	Electronic devices
Glick <i>et al</i> (1986)	USA	RCT	48	Hospital discharge patients	No	42	37	Time-limited partial hospitalisation programme	Non-specific intervention	Not keeping appointments after discharge	Medication compliance scale
Gomez Carrion <i>et al</i> (1993)	USA	CCT	48	Out-patients	No	55	56	Educational sessions about medication	Non-specific intervention	Not keeping appointments as scheduled	Case notes
Hayward <i>et al</i> (1995)	UK	RCT	4–8	Hospital discharge patients	No	10	11	Motivational interview psychotherapy	Non-specific intervention	Not taking medication as prescribed	Three-point scale
Hornung <i>et al</i> (1998)	Germany	CCT	48	Out-patients	No	84	64	Psychoeducational medication training	Non-specific intervention	Not taking medication as prescribed	Patient interview
Kelly & Scott (1990)	USA	RCT	24	Out-patients	No	314	104	Health education	Usual care	Not taking medication as prescribed	Patient interview
Kemp <i>et al</i> (1996)	UK	RCT	72	In-patients	No	39	35	Cognitive psychotherapy	Non-specific intervention	Not taking medication as prescribed	Adherence scale
Kopelowicz <i>et al</i> (1998)	USA	RCT	NS	Hospital discharge patients	No	28	31	Community re-enter educational programme	Non-specific intervention	Non-attendance at first post-discharge appointment	Case notes

(continued)

Table 1 (continued)

Study	Country	Design	Duration (months)	Setting	Special population of patients	Sample size (n)		Description of experimental intervention	Description of control intervention	Study end-point	Method used to assess non-adherence
						Experimental group	Control group				
Masnik <i>et al</i> (1981)	USA	CCT	24	Our-patients	Low-adherence patients	73	204	Seeing patients on a walk-in basis	Usual care	Non-attendance at appointments	Case notes
Olson <i>et al</i> (1998)	USA	CCT	NS	Hospital discharge patients	No	53	51	Pre-discharge out-patient clinician contact	Usual care	Non-attendance at first post-discharge appointment	Patient interview
Ran & Xiang (1995)	China	CCT	24	Our-patients	No	22	10	Psychoeducational family intervention	Usual care	Not taking medication as prescribed	Case notes
Robinson <i>et al</i> (1986)	USA	RCT	2	Hospital discharge patients	No	50	50	Educational sessions about medication	Usual care	Not taking medication as prescribed	Rating scale
Seltzer <i>et al</i> (1980)	Canada	CCT	20	In-patients	No	32	35	Educational group sessions about medication	Usual care	Not taking medication as prescribed	Urine test
Sharma <i>et al</i> (1995)	USA	CCT	NS	Hospital discharge patients	No	25	57	Pre-discharge out-patient clinician contact	Usual care	Non-attendance at first post-discharge appointment	Case notes
Shivack & Sullivan (1989)	USA	CCT	NS	Hospital discharge patients	No	221	439	Telephone call before scheduled appointments	Usual care	Non-attendance at first post-discharge appointment	Case notes
Sledge <i>et al</i> (1990)	USA	CCT	NS	Our-patients	First cases	34	115	Time-limited psychodynamic psychotherapy	Non-specific intervention	Dropping out during psychotherapy	Case notes
Stickney <i>et al</i> (1980)	USA	CCT	NS	Hospital discharge patients	No	200	200	Pre-discharge out-patient clinician contact	Non-specific intervention	Non-attendance at first post-discharge appointment	Case notes

(continued)

Table 1 (continued)

Study	Country	Design	Duration (months)	Setting	Special population of patients	Sample size (n)		Description of experimental intervention	Description of control intervention	Study end-point	Method used to assess non-adherence
						Experimental group	Control group				
Strang <i>et al</i> (1981)	USA	RCT	6	Out-patients	No	17	15	Family therapy	Non-specific intervention	Not taking medication as prescribed	Plasma level
Xiang <i>et al</i> (1994)	China	RCT	16	Out-patients	No	36	41	Psychoeducational family intervention	Usual care	Not taking medication as prescribed	Case notes
Xiong <i>et al</i> (1994)	China	RCT	72	Out-patients	No	34	29	Psychoeducational family intervention	Usual care	Not taking medication as prescribed	Patient interview
Youssef (1984)	Egypt	RCT	24	Hospital discharge patients	No	18	18	Educational sessions about medication	Usual care	Not taking medication as prescribed	Pill counts
Zhang <i>et al</i> (1994)	China	RCT	72	Out-patients	First cases	42	41	Psychoeducational family intervention	Usual care	Not taking medication as prescribed	Case notes

CCT, controlled clinical trial; RCT, randomised controlled trial; NS, not specified.

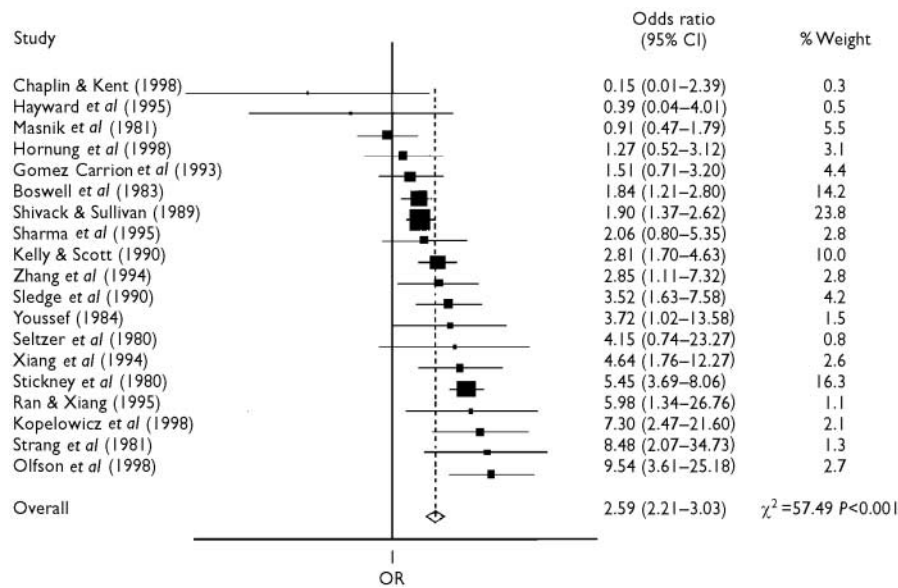


Fig. 1 Meta-analysis of studies assessing the effect of interventions for improving adherence: overall treatment effect for dichotomous outcomes. Odds ratio (OR) > 1 favours experimental interventions; OR < 1 favours usual care.

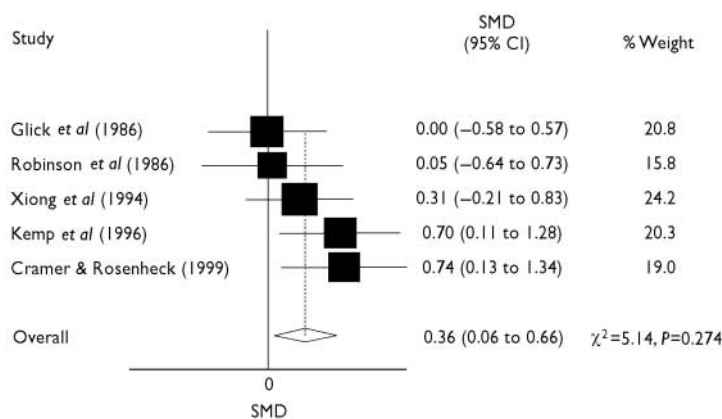


Fig. 2 Meta-analysis of studies assessing the effect of interventions for improving adherence: overall treatment effect for continuous outcomes. Standardised mean difference (SMD) > 0 favours experimental interventions; SMD < 0 favours usual care.

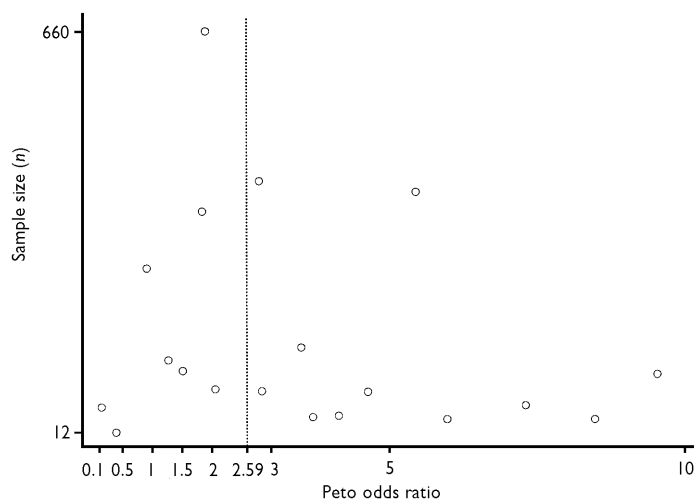


Fig. 3 Funnel plot of estimated odds ratio against the size of the study. The broken vertical line represents the overall intervention estimate.

scientific evidence, for reducing patient non-adherence. The magnitude of the overall treatment estimate suggests that, after a median follow-up of 6 months, these interventions more than double the likelihood of adherence to psychotropic medications and to scheduled appointments. Chen (1991), who conducted a narrative review of clinical interventions in psychoses, recommended scheduling appointments before discharge from in-patient treatment, using prompts in the forms of letters and telephone calls to encourage patients to keep their appointments and offering education about treatment and medication. However, it is unclear whether these strategies are equally effective in reducing patient non-adherence. In our analysis all interventions were found to be more effective than control treatments, but with different magnitudes of effect. Differences, however, were observed in the univariate analysis only: in the meta-regression model no single intervention emerged as predictor of overall treatment effect. Although this finding might suggest that all interventions are similarly effective, caution should be adopted in drawing definitive conclusions. The number of studies supporting each intervention and the total number of patients included in the evaluation of each intervention were fairly different, raising issues of generalisability. For example, only two studies evaluated the effect of prompts, but they included more than 1000 patients; in contrast, two studies evaluating the effect of psychotherapeutic interventions included fewer than 200 patients. Evidence derived from small samples and generated in a few settings cannot be considered as robust as evidence derived from large samples recruited in a diverse range of settings. From this perspective, we found robust data supporting, for example, the implementation of specific service policies such as pre-discharge contacts between patients and the community team, or supporting educational interventions about treatment and medications. Only direct comparisons between different strategies for reducing patient non-adherence will clarify whether some interventions are more cost-effective than others.

In contrast with this meta-analysis, the review by Zygmunt *et al* (2002) showed that only a third of 39 identified studies reported significant intervention effects. However, that review included only studies assessing the effect of interventions for reducing medication non-adherence. In

Table 2 Odds ratios of subgroup analyses of studies assessing the effect of interventions for reducing non-adherence

Study characteristic	Patients (n)	Studies ¹ (n)	Peto OR ²	(95% CI)
Design				
RCT	1119	9	2.60	(1.99–3.39)
CCT	2030	10	2.58	(2.12–3.14)
Length of follow-up				
< 6 months	1502	11	2.27	(1.78–2.90)
6+ months	324	3	1.70	(1.04–2.78)
Not applicable	1323	5	3.17	(2.52–3.99)
Diagnosis				
Schizophrenia only	537	7	3.21	(2.19–4.68)
Severe mental disorders	2612	12	2.47	(2.08–2.94)
Intervention				
Education	895	7	2.41	(1.72–3.37)
Psychotherapy	170	2	2.83	(1.36–5.87)
Prompts	1029	2	1.87	(1.45–2.42)
Service policies	863	4	3.63	(2.68–4.92)
Family therapy	192	4	4.45	(2.52–7.83)
Adherence to				
Appointments	2211	9	2.52	(2.10–3.02)
Medication	938	10	2.81	(2.03–3.88)
Setting				
In-patients	123	2	1.65	(0.38–7.18)
Out-patients	1664	10	2.16	(1.72–2.70)
Hospital discharge	1362	7	3.13	(2.50–3.91)

CCT, controlled clinical trial; RCT, randomised controlled trial.

1. Studies using dichotomous outcome data (n=19).

2. Odds ratio: OR > 1 favours experimental interventions; OR < 1 favours usual care.

Table 3 Predictive effect of study covariates on treatment outcome (meta-regression analysis)

Covariates	Coefficient ¹ (s.e.)	z	P ²
Randomised controlled trial ³	0.021 (1.173)	0.02	0.985
Length of follow-up			
< 6 months	Reference		
6+ months	−5.105 (1.620)	−3.15	0.002
Not applicable	1.490 (2.568)	0.58	0.562
Schizophrenia ³	3.802 (1.429)	2.66	0.008
Intervention			
Education	Reference		
Psychotherapy	−0.598 (1.994)	−0.30	0.764
Prompts	−1.862 (2.036)	−0.91	0.361
Service policies	−0.522 (1.904)	−0.27	0.784
Family therapy	1.349 (1.550)	0.87	0.384
Adherence to medication ³	−0.438 (1.750)	−0.25	0.802
Hospital discharge ³	−0.077 (2.021)	−0.04	0.969
Constant term	3.449 (3.334)	1.03	0.301

1. Positive coefficients indicate that covariates included in the meta-regression model were associated with a more favourable treatment outcome; negative coefficients indicate that covariates included in the meta-regression model were associated with a less favourable treatment outcome.

2. Values in bold are significant at $P < 0.05$.

3. Scored: 0, no; 1, yes.

our review, studies assessing the effect of interventions for improving adherence to scheduled appointments were included. Zygumunt *et al* (2002) included only studies of highly selected populations of people with schizophrenia, whereas we included non-selected populations of patients with psychosis. In addition, only studies in which adherence was one of the primary outcome measures were included in our analysis, whereas Zygumunt *et al* (2002) included studies in which adherence was not one of the primary end-points. These differences may explain their negative conclusions, as suggested by the evidence that studies where adherence was the central goal of the study provided positive results (Zygumunt *et al*, 2002). In some cases (for example, studies focusing on interventions not specifically developed for improving adherence), the decision whether adherence was one of the primary outcome measures or an ancillary variable was somewhat arbitrary. However, in most cases study authors clearly stated that the intervention was tested with the central goal of improving adherence (Bush *et al*, 1990; Xiang *et al*, 1994; Ran & Xiang, 1995; Dixon *et al*, 1997). We included only studies with a control group of patients receiving usual care, but Zygumunt *et al* (2002) did not exclude direct comparisons of different active strategies for improving medication adherence, such as behavioural management *v.* intensive case management, or psychoeducation plus family therapy *v.* psychoeducation plus relatives' groups; in only some of these direct comparisons was there a control group receiving standard care. Finally, the meta-analytic technique we employed to re-analyse outcome data systematically excluded studies without data suitable for re-analysis. Taken together, these differences may have overemphasised the treatment effect found in our analysis and explain the negative conclusions reached by Zygumunt *et al* (2002).

Long-term effect of interventions for reducing non-adherence

A second issue, relevant from a clinical viewpoint, is the long-term benefit of these interventions. Most of the included studies showed a positive effect soon after the implementation of the intervention for reducing non-adherence, but only a minority assessed whether the effect was maintained in the long term. In the meta-regression model, length of follow-up was

negatively associated with treatment effect, suggesting that the benefit of the interventions is less evident with increasing length of follow-up. Until long-term data become available and until studies establish which intervention maintains its effect in the long term, clinical interventions should be implemented in practice as short-term measures. For example, orientation and education about treatment and medications is essential to keep patients in treatment, but this intervention should be frequently and routinely repeated in the same patients, because it is unknown whether its effect is maintained in the long term. Similarly, pre-discharge contacts between patients and the out-patient team, or pre-discharge psychotherapeutic interventions, must become a routinely delivered service policy, offered each time patients are scheduled for discharge, even for patients who have already received it during previous admissions. In some community psychiatric services this goal is achieved by mixing in-patient and out-patient staff, so that in-patients are treated by the same team who will eventually offer out-patient care. This policy, which allows pre-discharge patient-staff contacts and the implementation of therapeutic plans before hospital discharge, has been shown to be associated with high rates of patient adherence in the long term (Sytema *et al*, 1997).

Diagnostic issues

A third issue is that patients with psychosis are a rather heterogeneous group. In many studies this diagnosis was adopted to collect representative samples of patients seen in everyday practice, including not only those with schizophrenia and related disorders, but also those showing psychotic features requiring the use of antipsychotic drugs. In some cases ambiguous diagnostic definitions were adopted, leading to the inclusion of patients with schizophrenia and with other unspecified diagnostic characteristics. It is possible that inclusion of these patients has increased the generalisability of study findings, since in everyday conditions many typical patients do not precisely fulfil diagnostic criteria of schizophrenia. Rather than relying on diagnostic criteria only, therefore, it might be useful to include in studies patients who are clinically or epidemiologically representative (Thorncroft & Tansella, 2002). These patients need to be characterised using valid and reliable

descriptors, and in most studies this description is currently lacking.

It is possible that interventions suitable for those with schizophrenia might not be suitable for other patients. In the meta-regression model we found that studies enrolling only homogeneous samples of people with schizophrenia were associated with a more favourable treatment effect, suggesting that these interventions are less effective in patients with other diagnoses. Similar findings emerged for other patient populations. Pampallona *et al* (2002), who performed a systematic review of patient adherence in the treatment of depression, showed that studies on adherence did not provide either reliable or consistent indications as to the efficacy of specific interventions. It is possible that psycho-educational or cognitive interventions, developed for patients with schizophrenia and for family members of those with schizophrenia, are not easily transferred to other categories of patients and family members with the same positive results.

Adherence to medication v. adherence to scheduled appointments

The magnitude of effect of interventions developed for improving adherence to medication was similar to that of interventions developed for improving adherence to scheduled appointments. We acknowledge the difficulty of making a clear distinction between these two categories, which were in many cases ambiguous and somewhat artificial. Patients not wishing to take the prescribed medicines might miss the scheduled appointments. Similarly, patients who want to discontinue the contact with the community psychiatric service might also stop taking the prescribed medicines. It might therefore be speculated that failing to adhere to treatment programmes is a patient characteristic that might result either in dropping out of treatment or in discontinuing the medicines, or both. There is nothing in the literature to show that there are two distinct categories of non-adherent patients, according to the definition of non-adherence. In other words, the concept of non-adherence might be unified and considered as one patient-related variable which can be measured and defined in many different ways.

Studies published before 1980

A limitation of this analysis is the exclusion of study reports published before 1980. This exclusion criterion was imposed for the purpose of generating evidence easily applicable to the modern organisation of community psychiatric services. Most studies before 1980 recruited patients resident in psychiatric hospitals and assessed strategies for reducing non-adherence to in-patient treatment regimens, or assessed compliance with out-patient programmes implemented in a hospital-based context of care where community facilities were lacking (Cramer & Rosenheck, 1998). In contrast, after 1980 many countries developed community-oriented systems of psychiatric care, with a diminished emphasis on psychiatric hospitals and a high priority given to out-patient care delivered by community mental health centres (Mosher & Burti, 1994). Continuity of care has thus become a basic quality requirement, essential to follow patients in their own context of life for a long time. We acknowledge that in our approach we might have missed some studies conducted in a community-oriented setting before 1980; however, this choice allowed us to pool data derived from a group of psychiatric services with a homogeneous commitment and a common mission. The exclusion of studies assessing adherence at initial appointments was based on similar reasoning: these constituted a separate group of studies, in which the main issue was not keeping contacts in the long term, but developing strategies for better psychiatric referral (Kluger & Karras, 1983).

Studies excluded from the meta-analysis

A second limitation is the exclusion of 23 studies because of the lack of information suitable for re-analysis. This represents a well-known source of potential bias when a quantitative approach is used in systematic reviews. The funnel plot of included studies was not symmetrical, suggesting that some studies might have been missed, for example small, negative studies (Fig. 3). These studies might be those not reporting absolute numbers or, possibly, those published in non-English-language journals. Their exclusion might have overemphasised the overall effect. To decrease this possibility two approaches were adopted. First, we always attempted to infer absolute numbers from percentages

reported in study tables; this was only feasible with a high degree of confidence in four cases, since in the others reviewers did not reach an agreement on the exact numbers to extract. Second, excluded studies were compared with the included ones and information on each study outcome was qualitatively extracted in agreement with what was reported by the study authors. The evidence that the proportion of reports with positive findings was similar in the two groups of studies did not corroborate (although not completely excluding) the possibility of selection bias.

Definition of adherence

Studies adopting different definitions of non-adherence and different methods of assessing non-adherence were grouped together. These differences are explained by the characteristics of the interventions under scrutiny: for example, studies evaluating prompts in the form of telephone calls adopted operational definitions of non-adherence such as non-attendance at appointments, whereas studies evaluating educational strategies on medications and side-effects measured the proportion of patients taking psychotropic drugs as prescribed. In some cases, however, the same interventions were evaluated using different definitions, for example studies assessing adherence after hospital discharge adopted definitions such as attendance at first outpatient appointment, attendance at five outpatient appointments, or attendance at a predefined proportion of appointments during follow-up. Only in a minority of studies were rating scales employed. These differences represent study limitations that might have been responsible for some between-study heterogeneity observed in the meta-analysis. The meta-regression model could have investigated this potential source of heterogeneity, but this approach was not used because it would have inevitably decreased the power of the analysis, generating findings of uncertain clinical relevance.

Recommendations

Much is still to be done in the field of treatment adherence in patients with schizophrenia and severe mental disorders. Experimental studies have to address the effectiveness of educational strategies, psychotherapeutic programmes and specific service policies in large samples of patients recruited in many different settings and

followed in the long term. Patients with schizophrenia should be considered separately from those with other diagnoses. Trials must adopt a high standard in terms of conduct and reporting: exclusion rates and reasons for exclusion should always be reported, as well as the proportion of patients failing to adhere to treatment at the end of the acute phase and the proportion of patients remaining adherent at follow-up. Absolute numbers should be given, avoiding the use of percentages without reporting the denominator to which they refer. Outcome data have to be reported for both completer and intention-to-treat samples.

APPENDIX I

Potentially relevant studies identified by the electronic search and subsequently excluded from the meta-analysis

- Atkinson, J. M., Coia, D. A., Gilmour, W. H., et al (1996)** The impact of education groups for people with schizophrenia on social functioning and quality of life. *British Journal of Psychiatry*, **168**, 199–204.
- Battle, E. H., Halliburton, A. & Wallston, K. A. (1982)** Self medication among psychiatric patients and adherence after discharge. *Journal of Psychosocial Nursing Mental Health Service*, **20**, 21–28.
- Blake, D. D., Owens, M. D. & Keane, T. M. (1990)** Increasing group attendance on a psychiatric unit: an alternating treatments design comparison. *Journal of Behavioural Therapy and Experimental Psychiatry*, **21**, 15–20.
- Boczkowski, J. A., Zeichner, A. & DeSanto, N. (1985)** Neuroleptic compliance among schizophrenic outpatients: an intervention outcome report. *Journal of Consulting and Clinical Psychology*, **53**, 666–671.
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APPENDIX 2

Randomised controlled trials and controlled clinical trials included in the meta-analysis

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CLINICAL IMPLICATIONS

- A large variety of clinical interventions have been studied to reduce non-adherence to treatment in patients with psychoses.
- After a median follow-up of 6 months these interventions more than double the likelihood of adherence to psychotropic medications and to scheduled appointments.
- The long-term benefit of clinical interventions for reducing treatment non-adherence in psychoses has still to be documented.

LIMITATIONS

- The studies included adopted different definitions and different measures of non-adherence.
- The exclusion of 23 studies not reporting information suitable for re-analysis represents a potential source of bias.
- Studies published before 1980 were not included.

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