Patient adherence in the treatment of depression

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Background Non-adherence with antidepressant treatment is very common. Increasing adherence to pharmacological treatment may affect response rate.

Aims To review and summarise quantitative evidence on factors associated with adherence and of adherence-enhancing interventions.

Method A systematic review of computerised databases was carried out to identify quantitative studies of adherence in depression. Papers retained addressed unipolar depression and considered adherence as the primary end-point.

Results Of studies published between 1973 and 1999, 32 met the review criteria: epidemiological descriptive studies (n=14): non-random comparisons of control and intervention groups (n=3); randomised interventions (n=14); and meta-analysis (n=1). Patient education and medication clinics were the interventions most commonly tested, combined with a variety of other interventions.

Conclusions The studies did not give consistent indications of which interventions may be effective. Carefully designed clinical trials are needed to clarify the effect of single and combined interventions.

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Adherence may be defined as the extent to which a person's behaviour conforms to medical or health advice (Bruer, 1982). Four meta-analyses (Anderson & Tomenson, 1995; Montgomery & Kasper, 1995; Steffens *et al*, 1997; Anderson, 1998) have demonstrated that for tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), drop-out rates are in the range of 21–33%, irrespective of the drug class. A subsequent meta-analysis showed that 20% of patients did not improve and 30% dropped out of treatment for a variety of reasons (Bollini *et al*, 1999). The drop-out rate is contributed to by factors such as illness and patients' characteristics, side-effects, time taken to improve or the patient–doctor relationship (Demyttenaere, 1997). The magnitude and complexity of the problem prompted this review of the available literature. The aim was to collect and synthesise quantitative information concerning factors associated with and interventions affecting adherence to antidepressants.

METHOD

Identification of relevant publications

In order to obtain the most exhaustive yield of papers addressing adherence in the treatment of depression, we first explored general textbooks on depression and on treatment adherence. Subsequently, multiple systematic searches of Medline, Current Contents, PsychInfo, and the Cochrane Collaborative Register of Trials were performed, restricted to the period from January 1990 to December 1999. The searches included the following medical subject headings: patient compliance, depressive disorders, psychotherapy, mental health services, randomised clinical trials, prospective studies, research designs and meta-analysis. About 5000 publications were identified. In addition, a systematic scrutiny of all the references of all the papers retrieved provided additional relevant studies. A total of 381 articles were judged potentially eligible for this review and read independently by two of us. The criteria to retain a publication were: that it addressed unipolar depression (either as the exclusive diagnostic category or as a substantial part of the diagnoses) and considered adherence rate (as opposed to response rate) as a primary end-point. The selected studies were classified into five mutually exclusive categories, according to the structure and informative content of each paper:

(a) descriptive epidemiological study, addressing factors associated with adherence;

(b) non-randomised intervention;

(c) randomised intervention (both (b) and (c) aimed at testing the effectiveness of interventions to improve adherence);

(d) meta-analysis;

(e) qualitative articles, such as editorials or review papers.

This report focuses on publications in categories (a)–(d).

Data extraction and synthesis

For all types of study we developed an *ad hoc* data extraction form. The main information extracted concerned the setting of the study, a clinical and demographic description of the patient sample, the length of the observation, response rate, adherence rate and the factors associated with adherence (for descriptive epidemiological studies only). As concerns adherence data, each study applied its own definition and rates were extracted as reported in the original publications. The measures of adherence were grouped into five categories:

(a) appointments kept (whether patients respected a pre-set schedule of visits);

(b) pills taken (any measure of adherence based on direct count of pills actually taken);

(c) plasma levels (any parameter measuring concentration of drug in blood);

(d) protocol deviation (termination of treatment before planned treatment period);

(e) composite index (*ad hoc* composite scales comprising any measure of intake of drug *and* other indicators such as patient satisfaction, reasons for stopping treatment, knowledge about drugs, satisfaction with treatment, etc.).

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The methodological strength of the papers was evaluated on the basis of whether the sample size computations were reported. This aspect is of relevance since the smaller the expected difference in adherence rate among subgroups (for descriptive epidemiological studies) or between treatment arms (for non-randomised and randomised intervention studies) the larger the sample size should be for there to be a reasonable chance of detecting it. For randomised intervention studies we also considered whether a description of the randomisation procedure was reported.

For non-randomised and randomised studies we grouped the interventions into seven categories: (a) psychological treatment; (b) patient education; (c) education of the patient's family; (d) training of physicians; (e) training of nurses; (f) changes in patient management (e.g. case management, change in the frequency of follow-up, etc.); and (g) medication clinics (scheduled meetings with the patient to adjust medication and control side-effects). Given the multi-modality of the interventions, we adopted the following approach to assess the relative effect on adherence of their components. First, all pairwise comparisons for every trial were constructed. Two-arm trials therefore contributed one pairwise comparison each: trials that compared three arms (say arms A, B and C) contributed three pairwise comparisons (namely A *v.* B, A *v.* C and B *v.* C). Similarly, the single trial with four arms contributed six pairwise comparisons. Subsequently, we defined as offset of a pairwise comparison the component of the intervention common to both arms being compared. For instance, a trial where drug treatment plus education of patients was compared with drug treatment alone was classified as having drug treatment as an offset. We defined as contrast the actual interventions being compared ignoring the common offset. For the same example, the contrast would be patient education *v.* no intervention.

Data were extracted and reviewed by two of us (S.P. & P.B.), and disagreements resolved with discussion. An *ad hoc* database was created for the data extracted, linked to a commercial database containing all the relevant references. Given the nature of the material found, no formal meta-analytical approach was justified, and no specific statistical analysis tools have been used.

RESULTS

Characteristics of the studies

All the sources considered provided a total of 32 eligible studies published between 1973 and 1999. Epidemiological descriptive studies accounted for 14 of the reviewed studies; three studies were non-randomised comparisons and randomised interventions accounted for 14 studies. Only one meta-analysis was retained. Almost half of the studies were conducted in the USA, and 10 in the UK. Three other studies were conducted in Canada, and three in Europe. About two-thirds of the descriptive and randomised studies, respectively, were published in the 1990s.

The studies reviewed were conducted in a variety of settings, with the majority taking place in out-patient psychiatric services (n=12) and psychiatric hospitals (n=8), and the remainder in primary care settings. The diagnostic categories employed in the studies are reviewed in Table 1. The category 'mixed diagnoses with depression' includes studies that considered other diagnoses besides depression (schizophrenia, bipolar disorders, etc.). With regard to measures of adherence, a majority of studies employed direct measures of drug intake, that is, the number of pills taken. Epidemiological studies employed quite often the number of appointments kept. Finally, only four studies used composite measures of drug intake and other indices.

The duration of observation varied considerably, from 2 to 104 weeks. Overall, patients were observed for more than 24 weeks in eight studies out of 31 (the meta-analysis is excluded). The median duration of observation was 12 weeks.

Methodological strength of descriptive epidemiological studies, non-randomised and randomised intervention studies

Epidemiological studies considered a total of 10 119 patients, with sample sizes varying from 27 to 4052 subjects. Non-randomised studies totalled 190 subjects, with a range of 23 to 100 patients. Evidence from randomised studies – the best source of information – was based on only 2145 patients and sample size varied from 14 to 649, a median of 120 patients. Sample size computations were performed and adequately reported in only two

Table 1 Diagnostic category and adherence measure by study design (excluding the single meta-analysis)

Design	Diagnosis/measure of adherence	Studies (n)
Descriptive study	Major depression	2
	Minor and major depression	3
	Mixed diagnoses with depression	5
	Unspecified depressive disorder	4
Non-randomised intervention	Mixed diagnoses with depression	2
	Unspecified depressive disorder	1
Randomised intervention	Major depression	3
	Minor and major depression	2
	Mixed diagnoses with depression	3
	Unspecified depressive disorder	6
Total		31
Descriptive study	Appointments kept	5
	Pills taken	6
	Plasma levels	2
	Composite index(es)	1
Non-randomised intervention	Appointments kept	1
	Pills taken	2
Randomised intervention	Appointments kept	1
	Pills taken	8
	Plasma levels	1
	Protocol deviation	1
	Composite index(es)	3
Total		31

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Table 2 Factors associated with adherence in 14 descriptive epidemiological studies

Study	Factors associated with better adherence	Adherence (%)	Sample size
Voris *et al*, 1983	Not studied	35	100
Johnson, 1981	Not studied	68	112
Craig *et al*, 1974	Not studied	42	238
Engstrom, 1991	Not studied	74	27
Hall *et al*, 1990	Not studied	97	29
Melfi *et al*, 1998	Lack of relapse	30	4052
Maddox *et al*, 1994	Lack of severe side-effects	52	46
Croghan *et al*, 1997	Use of fluoxetine rather than other antidepressant drugs	44	1242
Last *et al*, 1985	High education, high IQ, good social adjustment	66	125
Robinson *et al*, 1995	No side-effects, previous use of antidepressants	51	164
Tedlow *et al*, 1996	Lower rates of narcissistic–histrionic personality disorders	87	210
Blouin *et al*, 1985	Female gender, referral to a private psychiatrist, current psychiatric treatment	59	468
Simon *et al*, 1993	Prescription by a psychiatrist, prescription of imipramine, nortriptyline, fluoxetine	41	2432
Matas *et al*, 1992	Married status, non-emergency referral, diagnosis other than personality disorder and substance abuse	82	874

Table 3 Three contrasts and corresponding offsets in three non-randomised clinical trials

Contrast	Offset	Comparisons (*n*)	% adherence
Education of patient *v.* no intervention	Drug treatment	1	82 *v.* 68
Psychological treatment *v.* no intervention	Drug treatment	1	73 *v.* 8
Psychological treatment plus education of patient *v.* no intervention	Drug treatment	1	66 *v.* 9

randomised studies, while none of the other papers, whether a descriptive epidemiological or non-randomised intervention study, mentioned the expected effect on adherence of the factors or of the interventions respectively. Only three of the randomised studies described explicitly the procedure for randomisation.

Descriptive epidemiological studies

The main results of the 14 descriptive studies reviewed are reported in Table 2. The table suggests a very wide range of adherence rates (from 30 to 97%, median 63%). Factors positively and significantly associated with increased adherence were reported in nine studies; no systematic pattern was disclosed from the study of the factors identified. The relationship between adherence and response was reported in only one study.

Non-randomised and randomised interventions

The three non-randomised studies were all two-arm trials, contributing three contrasts, one per study. Ten randomised interventions also had two arms each, thus contributing 10 comparisons. Three randomised studies compared three arms each, contributing a total of nine comparisons. Similarly, the single trial with four arms contributed six comparisons. Therefore, a total of 28 comparisons were available for evaluation. The combinations of contrasts and offsets studied in the 17 trials are reported in Tables 3 and 4. Adherence rates varied widely across studies. The interventions most commonly tested were patient education and medication clinics. However, two reasons prevented a formal quantitative assessment of their efficacy by means of meta-analysis: (a) the great variety of offsets; (b) the heterogeneous combination of other interventions, even among studies with the same offset. It was therefore not possible to combine homogeneous data across studies.

The six comparisons for which data were available comparing patient education with no intervention (with drug treatment only as the common offset) could, in theory, contribute to a pooled estimate of the effect of patient education. However, they showed such different adherence rates in the 'no intervention' group, that we felt any formal meta-analytical effort would not be meaningful.

As a final remark, it should be noted that in Tables 3 and 4 those arms without or with fewer interventions (irrespective of the offset) almost invariably showed lower adherence rates.

Meta-analyses

We identified only one relevant meta-analysis (Roter *et al*, 1998), reporting results of 135 studies published between 1977 and 1994 on different medical conditions and on a variety of treatment regimens. Thirteen studies on mental health were part of the meta-analysis, including two randomised trials in depression, which have been already reviewed above as part of the randomised interventions.

DISCUSSION

Interpretation of the results

This review had three main findings. First, it confirmed that adherence is a major problem in the treatment of depression. Although drugs are commonly considered a critical tool in the treatment of depression, evidence from descriptive epidemiological studies confirmed that about one in three patients could not complete treatment. Second, in spite of its magnitude and of its worrisome implications in terms of morbidity and disability, adherence has rarely been the object of specific research, especially when compared with the vast amount of studies on the effectiveness of antidepressant drugs. Third, the few quantitative studies on adherence (non-randomised and randomised interventions) do not provide either reliable or consistent indications as to the efficacy of specific interventions or combinations thereof. They do, however, consistently point in the direction that adherence can indeed be increased through interventions supporting the prescription of antidepressants.

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Table 4 Twenty-five comparisons and corresponding offsets in 14 randomised clinical trials

Contrast	Offset	Comparisons (*n*)	% adherence
Drug treatment *v.* drug treatment[1]	Education of patient	3	29 *v.* 44
			42 *v.* 44
			42 *v.* 29
	No intervention	1	55 *v.* 83
Education of patient *v.* education of patient[2]	Drug treatment	2	65 *v.* 65
			32 *v.* 34
Education of patient *v.* medication clinic	Drug treatment plus training of nurses	1	42 *v.* 65
Education of patient *v.* no intervention	Drug treatment	7[3]	65 *v.* 48
			65 *v.* 48
			32 *v.* 32
			34 *v.* 32
			88 *v.* 80
			61 *v.* 28
	Drug treatment plus training of nurses plus medication clinic	1	60 *v.* 65
Education of patient *v.* psychological treatment	Drug treatment	1	37 *v.* 22
Education of patient plus education of family plus patient management plus psychological treatment *v.* no intervention	Drug treatment	1	37 *v.* 22
Education of patient plus management changes plus medication clinic *v.* no intervention	Drug treatment	1	69 *v.* 44
Education of patient plus medication clinic *v.* no intervention	Drug treatment plus training of physicians	1	76 *v.* 50
Medication clinic *v.* no intervention	Drug treatment plus training of nurses plus education of patient	1	60 *v.* 41
Psychological treatment plus education of patient plus education of family plus medication clinic *v.* no intervention	Drug treatment plus training of physicians	1	70 *v.* 46
Training of nurses plus education of patient *v.* no intervention	Drug treatment	1	42 *v.* 36
Training of nurses plus education of patient plus medication clinic *v.* no intervention	Drug treatment	1	60 *v.* 36
Training of nurses plus medication clinic *v.* no intervention	Drug treatment	2	50 *v.* 55
			65 *v.* 36

1. This was a three-arm study, where patients were randomised to amitriptyline (or mianserin, if at risk of overdose) once-a-day drug treatment, three-times-a-day drug treatment, or whatever schedule they chose.
2. In one study patients were randomised to two different educational messages: information on either drug side-effects or beneficial drug effects. In the second study patients were randomised to two different ways of providing information: either an information sheet describing the class of medication patients were discharged on, or the same plus a review of the written information provided by a nurse or a psychologist.
3. One study did not report adherence results.

Quality of the evidence

It was not possible to extract meaningful indications on factors associated with non-adherence from epidemiological studies because each study considered its own set of potential predictors. Additionally, the important relationship between adherence and outcome of treatment has been evaluated only in one study. The methodological quality of the literature on medication adherence can be evaluated by means of a recently published scoring system (Nichol *et al*, 1999). This score has not been applied here because its items are oriented to the evaluation of pharmacological treatments through physical and laboratory measurements. The majority of the comparative studies that we considered presents interventions other than pharmacological, and would thus score very low. We therefore assessed the methodological strength of the papers considering sample size computation and randomisation procedure – the results pointed to the poor methodological strength of the available contributions.

Complexity of study design

Intervention studies, and in particular randomised clinical trials, investigated a variety of interventions to improve adherence. The exception was one study where the intervention to increase adherence involved the administration of amitriptyline *v.* fluoxetine. Many studies, by implementing several interventions at the same time, could not provide evidence on the separate effects of each of the components. This leaves unaddressed the questions on which is the effect of each component and whether all of them are needed in combination, a common problem in the adherence literature (Haynes *et al*, 1996). Even looking at contrasts, as we have done, does not help to disentangle the effect of each component. The concept of contrasts allows the identification of the 'unconfounded' components of each trial (Haynes *et al*, 1996), that is, of the difference in terms of

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interventions between two arms of a trial. However, the offset may act on adherence in both arms of the trial being compared and perhaps synergistically so with the unconfounded component. The role of the offset can, therefore, hardly be allowed for. To complicate matters, the same contrast may also be paired with different offsets across studies: depending on the offset, the magnitude of the effect attributable to a given contrast may therefore vary from study to study. Finally, the studies addressed both minor and major depression as well as mixed diagnoses, making it difficult to assess whether specific interventions were more appropriate for specific diagnostic groups. Tables 3 and 4 none the less contain a consistent trend: the arm with more interventions generally showed a higher adherence rate. This suggests that improvements in adherence rates can indeed be achieved through the kinds of intervention considered in the literature.

Recommendations

Much is still to be done in the field of treatment adherence in depressive disorders. Successive classes of antidepressant have only marginally increased the proportion of patients actually benefiting from pharmacological treatment (Greenberg & Fisher, 1997). It is unrealistic to hope that a new drug may by itself reduce substantially the big proportion of patients who do not adhere to treatment. Carefully designed clinical trials are therefore needed to clarify the effect of single and combined interventions on adherence, as well as to further investigate the factors affecting adherence. Such studies and the proposed interventions should be feasible in busy clinical practices where the majority of patients are seen (Kendrick, 2000) and where adherence problems may be even more acute than in the setting of the common therapeutic clinical trials. Increasing the number of patients who are put in a position to better adhere to the prescribed treatment could in turn increase the response rate to antidepressant drugs (Haynes *et al*, 1996).

CLINICAL IMPLICATIONS

- A large variety and combinations of interventions have been proposed by the investigations considered in this review.
- No clear indication has emerged concerning which specific interventions or combinations thereof contribute to improve adherence, though evidence suggests that it can be improved.
- Further research should address both the causes of non-adherence to antidepressant drugs and the interventions affecting it.

LIMITATIONS

- The studies considered applied different measures of adherence including: bedside pill counts or blood drug levels, behavioural indicators, psychological symptoms, subjective evaluations or adherence to a pre-defined schedule of appointments.
- The possible relationship between the non-adherence rate and drug regimen (dose, duration, side-effects, etc.) could not be addressed given the design of the investigations considered in this review.
- This review does not provide evidence on whether an increase in adherence corresponds to an increase in response rate.

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APPENDIX – STUDIES REVIEWED

Meta-analysis

Roter, D. L., Hall, J. A., Merisca, R., *et al* (1998) Effectiveness of interventions to improve patient compliance. *Medical Care*, **36**, 1138–1161.

Descriptive studies

Blouin, A., Perez, E. & Minoletti, A. (1985) Compliance to referrals from the psychiatric emergency room. *Canadian Journal of Psychiatry*, **30**, 103–106.

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Croghan, T. W., Lair, T. J., Engelhart, L., *et al* (1997) Effect of antidepressant therapy on health care utilization and costs in primary care. *Psychiatric Services*, **48**, 1420–1426.

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Hall, D., Wiles, D. H. & McCreadie, R. G. (1990) Compliance with antidepressant medication (letter). *British Journal of Psychiatry*, **157**, 453–454.

Johnson, D. A. W. (1981) Depression: treatment compliance in general practice. *Acta Psychiatrica Scandinavica*, **290** (suppl. 63), 447–453.

Last, C. G., Thase, M. E., Hersen, M., *et al* (1985) Patterns of attrition for psychosocial and pharmacologic treatments of depression. *Journal of Clinical Psychiatry*, **46**, 361–366.

Maddox, J. C., Levi, M. & Thompson, C. (1994) The compliance with antidepressants in general practice. *Journal of Psychopharmacology*, **8**, 48–53.

Matas, M., Staley, D. & Griffin, W. (1992) A profile of the noncompliant patient: a thirty-month review of outpatient psychiatry referrals. *General Hospital Psychiatry*, **14**, 124–130.

Melfi, C. A., Chawla, A. J. Croghan, T. W., *et al* (1998) The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Archives of General Psychiatry*, **55**, 1128–1132.

Robinson, P., Bush, T., Von Korff, M., *et al* (1995) Primary care physician use of cognitive behavioral techniques with depressed patients. *Journal of Family Practice*, **40**, 352–357.

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Non-randomised interventions

Daley, D. C., Salloum, I. M., Zuckoff, A., *et al* (1998) Increasing treatment adherence among outpatients with depression and cocaine dependence: results of a pilot study. *American Journal of Psychiatry*, **155**, 1611–1613.

Myers, E. D. & Calvert, E. J. (1976) The effect of forewarning on the occurrence of side-effects and discontinuance of medication in patients on dothiepin. *International Journal of Medical Research*, **4**, 237–240.

Seltzer, A., Roncari, I. & Garfinkel, P. (1980) Effect of patient education on medication compliance. *Canadian Journal of Psychiatry*, **25**, 638–645.

Randomised interventions

Altamura, A. C. & Mauri, M. (1985) Plasma concentrations, information and therapy adherence during long-term treatment with antidepressants. *British Journal of Clinical Pharmacology*, **20**, 714–716.

Demyttenaere, K., Van Ganse, E., Gregoire, J., *et al* (1998) Compliance in depressed patients treated with fluoxetine or amitriptyline. *International Clinical Psychopharmacology*, **13**, 11–17.

Katon, W., Von Korff, M., Lin, E., *et al* (1995) Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *Journal of the American Medical Association*, **273**, 1026–1031.

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