Improving Adherence to Antidepressants: A Systematic Review of Interventions

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Background: Effectiveness of antidepressant medication is reduced by patients' nonadherence. Several interventions to improve adherence in patients diagnosed with unipolar depression have been tested.

Objective: To systematically review the effectiveness of interventions that aimed to improve adherence to antidepressant medication in patients with unipolar depression.

Method: Systematic review of English-language articles of randomized controlled trials obtained by a computerized literature search of MEDLINE (1966–January 2002) using the terms *patient compliance*, *patient dropout*, *treatment refusal*, *patient education*, *adherence*, *clinical trial*, *randomized controlled trial*, *controlled trial*, *depressive disorder*, and *depression*; PSYCINFO (1984–January 2002) using the terms *random*, *clinical*, *control*, *trial*, *adherence*, *compliance*, *noncompliance*, *dropouts*, *patient education*, *depression*, *major depression*, *affective disorders*, and *dysthymic disorder*; EMBASE (1980–January 2002) using the terms *patient compliance*, *patient dropouts*, *illness behavior*, *treatment refusal*, *patient education*, *clinical trial*, *controlled study*, *randomized controlled trial*, and *depression*; and the Cochrane Controlled Trials Register (no restrictions) using the terms *random**, *complian**, *adheren**, *pharmacotherapy*, *regimen**, *educat**, *medicat**, *depression*, and *depressive disorder*.

Results: Educational interventions to enhance adherence failed to demonstrate a clear benefit on adherence and depression outcome. However, collaborative care interventions tested in primary care demonstrated significant improvements in adherence during the acute and continuation phase of treatment and were associated with clinical benefit, especially in patients suffering from major depression who were prescribed adequate dosages of antidepressant medication.

Conclusion: We found evidence to support the introduction of interventions to enhance adherence with antidepressant medication in primary care, not only because of better adherence but also because of better treatment results. Because collaborative care interventions require additional resources, a better understanding of the mode of action of different programs is needed to reduce avoidable costs. The effectiveness of educational interventions needs more evidence.

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Depressive illness is a public health issue of major significance.[1] Lifetime prevalence is estimated at about 15%,[2] and most depressive patients are treated in general practice.[3,4] Despite proven efficacy of antidepressant medication, many depressed patients do not receive an adequate dosage and duration of treatment.[5] Shortcomings in depression treatment are frequently noted in both primary care and specialized care.[6] These may result in serious consequences such as treatment failure, chronic course, complications, high medical care utilization, and impairment in work functioning and other activities.[7,8] Effectiveness of antidepressants is also reduced by patients' nonadherence. Observational studies found discontinuation rates of 28% at 1 month and 44% to 52% at 3 months.[9,10]

Adherence to antidepressant medication is essential to the outcome of depression treatment. However, Haynes et al.[11] concluded, in a review of interventions to enhance adherence in chronic illnesses like asthma, hypertension, and schizophrenia, that current interventions are not very effective. Studies of programs that aimed to improve adherence with antidepressants were not included. In depressive disorders, education and active participation of patients in the treatment process were presented as cornerstones to enhancing treatment adherence.[12] Other investigators argued that multifaceted interventions targeting patient, physician, and structural aspects of care have the potential to improve adherence and depression outcome.[13]

Recently, 2 review articles on adherence to antidepressant medication were published.[14,15] There are a number of significant shortcomings in these articles, however.

Pampallona et al.[14] included several studies of patients suffering from psychiatric disorders not limited to unipolar depressive disorders who were treated with different classes of psychotropic medication,[16–19] as well as a study investigating adherence to referral but not adherence to medication.[19] The authors did not give important details on characteristics of the reviewed studies, and results of a statistical comparison of adherence outcomes between groups were not reported. Lingam and Scott[15] included only 2 randomized controlled trials of interventions aiming to improve adherence with antidepressant medication in patients with unipolar depressive disorders.[13,20] Although adherence is a means to an end,[21] these 2 reviews did not report on depression outcome.

In view of the shortcomings of the previous reviews, we decided to review the randomized controlled trials on interventions to improve adherence with antidepressants from the perspective of the studies and to report on effectiveness, adherence, and depression outcome.

The objective of the review was to explore the effectiveness of interventions that aimed to improve adherence with antidepressive agents in patients with unipolar depression.

METHOD

The studies used for this systematic review were obtained by a computerized literature search of 4 databases. The search strategy was as follows:

MEDLINE (1966–January 2002): Boolean searches and search terms used were "(*patient compliance* OR *patient dropout* OR *treatment refusal* OR *patient education* OR *adherence*) AND (*clinical trial* OR *randomized controlled trial* OR *controlled trial*) AND (*depressive disorder* OR *depression*)" (all fields).

PSYCINFO (1984–January 2002): Boolean searches and search terms used were "(*random* OR *clinical* OR *control* OR *trial*) AND (*adherence* OR *compliance* OR *noncompliance* OR *dropouts* OR *patient education*) AND (*depression* OR *major depression* OR *affective disorders* OR *dysthymic disorder*)" (all fields).

EMBASE (1980–January 2002): Boolean searches and search terms used were "(*patient compliance* OR *patient dropouts* OR *illness behavior* OR *treatment refusal* OR *patient education*) AND (*clinical trial* OR *controlled study* OR *randomized controlled trial*) AND (*depression*)" (all fields).

Cochrane Controlled Trials Register: (no restrictions) Boolean searches and search terms used were "(*random**) AND (*complian** OR *adheren** OR *pharmacotherapy* OR *regimen** OR *educat**) AND (*medicat**) AND (*depression* OR *depressive disorder*)."

Additional reports were identified from the reference lists of retrieved reports and the review article of Pampallona et al.[14] Only English-language publications in peer-reviewed journals were considered for inclusion.

Articles were selected if they reported a randomized controlled trial of an intervention aimed at improving adherence to prescribed antidepressant medication in patients with unipolar depression. Studies on interventions that did not target the patient directly (e.g., studies of implementing practice guidelines or training physicians) were not included. No selection on quality of studies was made. Important methodological issues will be addressed in the discussion. Data extraction was done by 1 author (A.C.M.V.) and cross-checked by another author (A.B.).

RESULTS

The search strategy retrieved 21 studies. The study of Finley et al.[22] was not included because adherence rates were not yet available. Another identified study[23] reported on the 19-month follow-up of 2 studies included in this review.[13,24] This left 19 studies to be included.[13,20,24–40] The characteristics and results of the studies are shown in Table 1. More detailed information is available on request.

There were many differences across studies, preventing a quantitative comparison between groups. Results are therefore summarized qualitatively. We decided to discuss the studies performed in psychiatric outpatient clinics separately from those performed in primary care.

There were no studies of hospitalized depressive patients. Inclusion and exclusion criteria differed among studies, and assessment of depressive disorder was not uniform. The sample size of the studies ranged from 14 to 1356 participants. The total number of patients participating in the studies was 5232. The interventions were not uniform. We classified the studies into 2 broad categories of treatment modality: patient education and collaborative care.

Patient education ranged from notifying patients of possible side effects[25,26] to an information leaflet that was read and explained to the patient during the initial visit[28] and to personalized information mailed directly to patients.[31,32]

Collaborative care, on the other hand, was defined as a systematic approach that improves patient education and with an active role of mental health professionals or other care extenders, such as nurses, in primary care.[34] Collaborative care interventions are multimodal, i.e., affecting patient and physician as well as the system of care. Increased patient education, longer and more frequent visits, surveillance of adherence to medication regimens, primary care training in the treatment of depression, and feedback and recommendations given by care extenders were frequently used components.

Practice nurses aimed to enhance treatment adherence by discussion and encouragement—particularly by pro-

Table 1. Characteristics and Results of 19 Randomized Controlled Trials for Improving Adherence to Antidepressants in Patients With Unipolar Depression

Study	Intervention	Adherence[a] (intervention vs control groups)	Depression Outcome[a] (intervention vs control groups)
Psychiatric outpatient studies			
Myers and Calvert[25]	Education	NS	Not reported
Myers and Calvert[26]	Education	NS	Not reported
Myers and Calvert[27]	Education	Combination verbal and written information > verbal information	Not reported
Myers and Calvert[28]	Education	NS	Not reported
Myers and Branthwaite[29]	Dosage regimen	Doctor-prescribed vs patient-chosen regimens: NS Dosage once a day vs three times a day: NS Patients who were allowed to choose and chose the 3-times-a-day regimen showed significantly better adherence	Not reported
Altamura and Mauri[30]	Education	Not reported	Intervention > usual care
Primary care studies			
Mundt et al[31]	Education	NS	NS
Atherton-Naj et al[32]	Education	NS	Intervention > usual care
Peveler et al[20]	Education	NS	Not reported
Peveler et al[20]	Collaborative care	Intervention > usual care	Patients with major depression and doses above 75 mg dothiepin > other patients
Wilkinson et al[33]	Collaborative care	NS	NS
Katon et al[13]	Collaborative care	Major depression: intervention > usual care Minor depression: intervention > usual care	Major depression: intervention > usual care Minor depression: NS
Katon et al[24]	Collaborative care	Major depression 4-month: intervention > usual care 7-month: trend for intervention > usual care (p = .07) Computerized data: NS Minor depression 4-month: intervention > usual care 7-month: intervention > usual care Computerized data: trend for intervention > usual care (p = .08)	Major depression: intervention > usual care Minor depression: NS
Katon et al[34]	Collaborative care	3-month: intervention > usual care 6-month: intervention > usual care Computerized data: intervention > usual care	3-month: intervention > usual care 6-month: trend intervention > usual care; (p = .08) Remission: 3-month: intervention > usual care 6-month: intervention > usual care
Katon et al[35]	Collaborative care	Intervention > usual care	Intervention > usual care Relapse: NS
Hunkeler et al[36]	Collaborative care	NS	Intervention > usual care
Katzelnick et al[37]	Collaborative care	Intervention > usual care	Intervention > usual care
Simon et al[38]	Collaborative care	Intervention > usual care	Intervention > usual care
Wells et al[39]	Collaborative care	Intervention > usual care	Intervention > usual care
Rost et al[40]	Collaborative care	Intervention > usual care	Intervention > usual care

[a]Significance set at $p \leq .05$.
Symbol: > = significantly better than.

viding explanation and reassurance about side effects of medication[33] or counseling that addressed daily routine, lifestyle, attitudes to treatment, and the reasons for treatment and by giving advice about the use of reminders and cues to take the medication.[20]

Telehealth care was also used. It consisted either of emotional support and focused behavioral interventions provided in ten 6-minute calls during 4 months by primary care nurses[36] or of assessments including current use of antidepressants, side effects, and severity of depressive symptoms and sometimes general support and encouragement by care managers in 2 phone calls. After each telephone assessment, doctors received a feedback report and treatment recommendations.[38]

Several interventions had an integrated role of the psychiatrist in primary care.[13,24,34,37] In one study,[38] the psychiatrist supervised the telehealth care case managers. Psychologists providing brief psychotherapy were integrated in one intervention.[24] In another study,[36] a psychologist supervised the practice nurses.

Control groups were treated with "usual care," meaning that no services other than the standard were provided to patients and doctors. In most cases, usual care for depression involved prescription of antidepressant medication and 2 to 3 visits over the first 3 months of treatment.[24] One study[20] also contained an attention control group. Patients in this group received only 1 interview to assess the effect of closer monitoring by the research team on adherence.

Assessment and definition of adherence were variable among the studies. While a recent study comparing methods of assessing adherence with medication found the electronic pill container, which records each opening of the container, to be the most informative,[41] only 1 study used electronic monitoring to check reliability of patient-reported adherence.[20] Fourteen studies reported the depression outcome.[13,20,24,30–40] Follow-up ranged from 2 weeks to 12 months. Percentage of study completers ranged from 38% to 100%.

ADHERENCE OUTCOME

Psychiatric Outpatient Studies

Five[25–28,30] of the 6[25–30] psychiatric outpatient studies tested education as an adherence-enhancing intervention, and 3 of these studies[25,26,28] failed to demonstrate differences in adherence between groups. Myers and Calvert[28] found a statistically significantly better adherence in the information group at week 3, but at week 6 this difference had disappeared. In another study, Myers and Calvert[27] demonstrated a significantly better adherence with medication in patients who received the combination of verbal and written information about side effects of antidepressant medication. The study by Altamura and Mauri[30] also reported a better adherence in the intervention group, but the statistical significance was not reported. The study by Myers and Branthwaite from 1992[29] was the only study that tested the influence of the number of doses to be taken per day and the effectiveness of allowing patients to choose their own dosage regimen. Adherence was significantly better in only those patients who were allowed to choose and selected the 3-times-a-day dosage.

Primary Care Studies

Of 13 primary care studies,[13,20,24,31–40]11 studies[13,20,24,33–40] tested a collaborative care intervention, and 3 studies[20,31,32] tested educational interventions. The study of Peveler et al.[20] had 3 intervention arms: (1) leaflet, (2) drug counseling by a nurse, and (3) leaflet and drug counseling by a nurse. The leaflet is considered an education intervention, and the drug counseling arms are considered collaborative interventions because general practitioners and nurses worked together.

Of the collaborative care studies,[13,20,24,33–40] 9 studies, including the counseling arms of the study of Peveler et al.,[20] showed significant differences in adherence between intervention and usual care groups.[13,20,24,34,35,37–40] In the intervention groups, adherence was approximately 25% higher than that in the usual care groups.[13,24] Rost et al.[40] found that the intervention increased pharmacotherapy use in patients beginning a new treatment episode but had no effect in recently treated patients. The studies of Wilkinson et al.[33] and Hunkeler et al.[36] failed to demonstrate a difference in adherence between the intervention and usual care groups. Simon et al.[38] found that an organized program, consisting of care monitoring, follow-up by telephone, feedback to doctors, and practice support by a care manager, resulted in significant improvements in antidepressant medication use and in a better clinical outcome. A program limited to monitoring and feedback, using computerized data (antidepressant dosage and repeat prescriptions, number of follow-up visits, and arranged visits), had no significant effect compared with usual care.

The studies of Mundt et al.[31] and Atherton-Naj et al.[32] and the leaflet arm in the study of Peveler et al.[20] tested an education intervention. All failed to demonstrate differences in adherence.

DEPRESSION OUTCOME

Psychiatric Outpatient Studies

Only 1 psychiatric outpatient study reported the depression outcome.[30] A significantly greater reduction in depression score was found in the intervention group.

Primary Care Studies

All primary care studies[13,20,24,30–40] measured depression outcome. Only 2 studies, 1 education study[31] and 1 collaborative care study,[33] failed to demonstrate a significant difference in depression outcome between groups. Rost et al.[40] demonstrated that the intervention increased improvement in depressive symptoms in patients beginning a new treatment episode, but not in recently treated patients. Peveler et al.[20] found clinical benefit only in patients with major depression and doses above 75 mg of dothiepin. Katon et al.[13,24] also demonstrated clinical benefit in patients with major depression but not minor depression.[42]

DISCUSSION

Searching for randomized controlled trials that evaluated interventions aiming to enhance adherence with antidepressant medication, we found 19 studies that met the inclusion criteria. The limitations of a qualitative review should be taken into account. Such reviews compare studies that are based on patients from different populations and different geographic locations and performed in varying time periods. Studies of interventions that did not target the patient directly (e.g., studies of implementing practice guidelines or training physicians) were not included. The impact of interventions to improve physicians' compliance with guidelines is quite relevant in itself but is not a topic of this review.

In the psychiatric outpatient studies, only educational interventions were tested. Only the study of Myers and Calvert,[27] which combined verbal with written information, resulted in a better adherence. It is, however, important to bear in mind that 2 of the studies of Myers and

Calvert[25,26] that failed to show differences in effect had a very short follow-up (2 weeks). The study of Altamura and Mauri[30] is methodologically flawed because it did not correct for other medication, which is indispensable when measuring drug levels, and only 14 patients were included. The meaning of the better depression outcome in the intervention group in the study of Altamura and Mauri[30] is unclear, given the aforementioned methodological limitations. The study of Myers and Branthwaite from 1992[29] did not analyze differences in depression outcome between the intervention groups but rather between adherent and nonadherent patients. There was no evidence that better adherence was associated with a better therapeutic result, possibly because those patients who were improving most tended to abstain from further treatment. Also, the prescribed dosages of antidepressant medication were rather low.

All primary care studies that tested educational interventions to enhance adherence failed to demonstrate a benefit over the control condition. However, the study of Atherton-Naj et al.[32] also had a small sample size (N = 45) that possibly precluded the finding of significant differences. The primary aim of this latter study was to investigate the feasibility of the intervention. The negative results of the study of Mundt et al.[31] particularly raise questions because this study included 246 patients, precluding a type II error. In this study, however, the intervention consisted of written time-phased educational information mailed directly to the patient that may have been too impersonal or too confronting. Such a procedure may cause a detrimental effect on adherence and possibly nullified the positive influence of education on adherence. Moreover, this study used an interactive voice-response telephone system to obtain assessment data and may thus have introduced another impersonal characteristic.

In primary care studies, 9 collaborative care interventions demonstrated significant improvements in rates of adherence during the acute and continuation phase of treatment (≥ 6 months). A pilot study to test the feasibility of the intervention[33] failed to demonstrate a better adherence in the intervention group. Probably this study was underpowered (N = 61). Hunkeler et al.[36] also failed to demonstrate a difference in adherence between intervention and control groups, while this study included 302 patients. All collaborative care studies in which a better adherence was achieved in the intervention groups compared with the control groups demonstrated better depression outcomes, especially in patients suffering from major depression. The study of Hunkeler et al.[36] also demonstrated significantly better depression outcome in the intervention group, despite the lack of difference in adherence to antidepressant medication between groups.

Most of the studies testing collaborative care interventions are multimodal, affecting patient, physician, and system of care, which makes it impossible to discern quality of care from patient behavior. In fact, these are integrally linked. These studies targeted both improving patient education and improving physician quality of care through lecture, reading materials, and appropriate feedback from nurses and mental health specialists working as primary care extenders. Probably the improvements in adequate antidepressant medication found in these studies resulted from a combination of improved quality of care (e.g., the prescribing of antidepressant was done more carefully) and the patients' adherence. More complex interventions were not tested in psychiatric outpatient clinics. These need further attention, because patients treated in specialty care differ from those treated in primary care.

In general, informed consent, repeated monitoring of patient status, and physicians' heightened awareness of nonadherence may have provided a prompt to continue treatment in both groups, thereby minimizing effects that might have occurred. Despite this, especially collaborative care interventions tested in primary care demonstrated significant improvements in rates of adherence and depression outcome during the acute and continuation phase of treatment (≥ 6 months). Given the poor methodology of the studies that tested patient education, the lack of evidence of effect certainly does not mean that there is no effect at all. For instance, the combination of verbal and written information about side effects of antidepressant medication resulted in a better adherence,[27] and patients reporting more educational messages concerning medication and discussions of behavioral strategies from their doctor were more likely to adhere to medication.[10]

The favorable findings regarding interventions to improve adherence with antidepressants are in contrast to the negative conclusion of the Haynes et al.[11] systematic review, as mentioned in the introduction. The inclusion criteria in that review were very strict (e.g., at least 80% follow-up of each group studied and, for long-term treatments, at least 6 months of follow-up with positive initial findings), and, as a consequence, the review included no study on interventions to improve adherence to antidepressants.

In conclusion, we found evidence to support the introduction of interventions to enhance the process of care of patients with major depression in primary care. Because collaborative care programs require additional resources,[43] the specificity of the interventions needs to be improved. It is recommended that future studies investigating interventions to improve adherence to antidepressant medication attempt to elicit the effects of individual components of the intervention in addition to the effect of the entire intervention.

Since some patients with major depression achieve a favorable outcome with usual care, a stepped-care strategy targeting only those patients whose depression has not resolved within a 2-month period of usual care may be a viable option.[34] This would involve targeting interven-

tions to patients with persistent symptoms. More evidence is also needed on the effectiveness of different forms of patient education, e.g., from well-designed randomized controlled trials.

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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For the CME Posttest for this article, see pages 1553–1554.