SYSTEMATIC REVIEW

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Editor's Choice

# Effectiveness of interventions to improve antidepressant medication adherence: a systematic review

W. W. Chong, P. Aslani, T. F. Chen

Faculty of Pharmacy, The University of Sydney, NSW, Australia

**Correspondence to:**
Wei Wen Chong, PhD Student, Faculty of Pharmacy, The University of Sydney, NSW 2006, Australia
Tel.: + 612 9036 9490
Fax: + 612 9351 4391
Email: weiwen.chong@sydney.edu.au

**Disclosures**
The authors have no sources of funding or conflicts of interest to declare.

**SUMMARY**

Non-adherence to antidepressant medications is a significant barrier to the successful treatment of depression in clinical practice. This review aims to systematically assess the effectiveness of interventions for improving antidepressant medication adherence among patients with unipolar depression, and to evaluate the effect of these interventions on depression clinical outcomes. MEDLINE, PsycINFO and EMBASE databases were searched for English-language randomised controlled trials published between January 1990 and December 2010 on interventions to improve antidepressant adherence. The impact of interventions on antidepressant medication adherence (compliance and persistence) and depression clinical outcomes was evaluated. Data concerning the quality of the included studies were also extracted. Twenty-six studies met the inclusion criteria. Interventions were classified as educational, behavioural and multifaceted interventions. A total of 28 interventions were tested, as two studies investigated two interventions each. Sixteen (57%) of the 28 interventions showed significant effects on antidepressant adherence outcomes, whereas 12 (43%) interventions demonstrated significant effects on both antidepressant adherence and depression outcomes. The interventions which showed significant improvement in outcomes were primarily multifaceted and complex, with proactive care management and involvement of mental health specialists. The most commonly used elements of multifaceted interventions included patient educational strategies, telephone follow-up to monitor patients' progress, as well as providing medication support and feedback to primary care providers. Overall, educational interventions alone were ineffective in improving antidepressant medication adherence. In conclusion, improving adherence to antidepressants requires a complex behavioural change and there is some evidence to support behavioural and multifaceted interventions as the most effective in improving antidepressant medication adherence and depression outcomes. More carefully designed and well-conducted studies are needed to clarify the effect of interventions in different patient populations and treatment settings.

**Review criteria**

A literature search was conducted using the MEDLINE, PsycINFO and EMBASE databases to identify randomised controlled trials of interventions to improve antidepressant adherence. A manual search was also performed on the reference lists of included studies, relevant reviews as well as the authors' personal files. Data concerning the type of intervention, adherence measures, adherence outcomes and depression clinical outcomes were extracted from included studies to enable comparison.

**Message for the clinic**

A systematic review of 26 studies indicated that the interventions that were successful in improving both antidepressant adherence and depression clinical outcomes were primarily multifaceted interventions that employed combinations of educational, behavioural, affective and provider-targeted strategies. Given the nature of depression as a chronic and recurrent illness, ongoing supportive services may be necessary especially at critical points of treatment. More rigorous and well-conducted studies are necessary to improve antidepressant compliance and persistence in a variety of patient populations and settings.

## Introduction

Depression is one of the most prevalent forms of mental disorder, with a high public health impact. It is expected that depression will become the second leading cause of disability worldwide by the year 2020 (1). Depression is frequently treated in primary care practice with antidepressant medications (2). Although antidepressants may be effective in the treatment of depression (3), patients' failure to take them as prescribed remains a significant obstacle to treatment success in clinical practice. The World Health Organization (WHO) has recognised depression as one of the nine chronic conditions to be focused on for improving medication adherence (4).

Adherence has been defined as 'the extent to which a person's behaviour coincides with the medical advice given' (5). Previous studies have highlighted two main aspects of adherence problems with antidepressants – the premature discontinuation of antidepressant therapy (also known as medication non-persistence) and the lack of consistency with the prescribed regimen in the context of ongoing use (medication non-compliance). Although treatment guidelines advocate the continuous use of antidepressants for at least



 
doi: 10.1111/j.1742-1241.2011.02746.x

6 months after full remission for all patients with major depression (6–8), nearly one-third of patients discontinue medications against medical advice in their first month of treatment (9). The premature discontinuation of antidepressant therapy has been linked to poor treatment outcomes such as increased risk of relapse and recurrence, as well as increased healthcare costs (10–12).

Medication non-compliance in the context of ongoing use is also a common problem with antidepressants. Patients may not conform to the recommendations made by the prescriber in terms of timing, dosage and frequency of medication taking (13). For example, patients may either intentionally or unintentionally miss doses, take extra doses, delay the timing of their doses or take drug holidays. This incomplete implementation of instructions from prescribers could also affect depression treatment outcomes, resulting in non-response or discontinuation symptoms (14). Furthermore, the consistency of patients' medication-taking behaviour influences their medication persistence, as early discontinuation is often preceded by a period of poor medication compliance (14).

Improving both aspects of antidepressant medication adherence has proved to be a challenging task. Although a variety of theoretical models (such as the Health Belief Model, Theory of Planned Behaviour and Stages of Change Model) (15–17) have been used to predict and change adherence, these models allow us to examine only the psychological focus from the patient's perspective. However, in addition to patient-related factors, there are also other factors affecting medication adherence such as the pharmacological characteristics of antidepressants, the illness characteristics, provider's behaviour and delivery of the healthcare system (18–20). Recognising this fact, most of the interventions designed to improve antidepressant medication adherence have been multifaceted, attempting to target the different dimensions affecting medication adherence.

Previous reviews have suggested that interventions employing combinations of strategies are more effective than single-component interventions in improving antidepressant medication adherence (21,22). However, the different aspects of medication adherence outlined above (compliance or persistence) were not studied in these reviews, nor were the key components of multifaceted interventions ascertained. Further studies have also been published since the last comprehensive review on this important area was performed in 2007 (23). The purpose of this review, therefore, was to systematically assess the effectiveness of interventions for improving patients' adherence to prescribed antidepressants, taking into account the gaps in information mentioned above. The secondary objective was to evaluate the effect of these interventions on depression clinical outcomes.

## Methods

A literature search was conducted using the MEDLINE, PsycINFO and EMBASE electronic databases. The search was limited to English-language studies published in peer-reviewed journals between January 1990 and December 2010. Keywords and medical subject headings used to identify relevant studies were: *patient compliance, medication adherence, persistence, concordance, patient dropouts, treatment refusal, discontinuation, termination, depression, depressive disorder, antidepressive agents, intervention, therapy, management, program* and *treatment outcomes*. (The full search strategy for MEDLINE database is provided in Appendix 1). We also searched the reference lists from all included studies and relevant reviews, as well as the authors' personal files to identify additional articles. A single researcher performed the initial systematic literature search by screening titles and abstracts. Full papers from potentially relevant studies were then retrieved and assessed for eligibility based on the inclusion criteria. Another researcher subsequently reviewed all included and excluded studies. Differences were resolved by further discussion among all the study authors.

### Inclusion criteria

The following selection criteria were used to identify studies to be included in this review: (i) the study reported a randomised controlled trial of at least one patient-focused intervention that aimed to improve adherence to prescribed antidepressants; (ii) the study evaluated samples of adult participants aged ≥ 18 years, with a primary diagnosis of unipolar depression and who had been prescribed antidepressants; (iii) a control group receiving usual care was included in the study; (iv) antidepressant medication adherence was one of the primary or secondary outcome measures reported; (v) the study reported at least one clinical outcome and (vi) the study had a follow-up period of at least 6 months.

The following types of studies were excluded: those describing interventions directed solely at clinicians to improve adherence to treatment guidelines; those that evaluated treatment adherence to other than antidepressant therapy (for example appointments kept, treatment referrals and psychotherapy); and those that did not adequately describe methods and results pertaining to antidepressant medication adherence.

### Data extraction and analysis

From each study that was included, the following information was extracted: country of publication, study setting, sample size, subject characteristics, antidepressant treatment characteristics, follow-up times, description of experimental and control intervention, type and components of the intervention, adherence measures, adherence outcomes and depression clinical outcomes.

We used the components of the Jadad scale to give an indication of the methodological quality of the included studies (24).The following quality criteria were extracted: process and unit of randomisation, blinding of outcomes assessment and loss to follow-up. We did not evaluate blinding of the patients as it was deemed not possible because of the nature of adherence interventions. In addition, we also evaluated whether a power calculation was reported in studies. Given the variability of the measures of adherence, interventions and outcomes of the studies, we were unable to use meta-analytic methods. Instead, results of the interventions were reviewed and compared qualitatively.

### Classification of interventions

Interventions were grouped into broad categories based on the classification employed by Roter and colleagues (25), and another study which employed a similar classification (26). These categories (educational, behavioural, affective or provider-targeted) reflect the differences in the theoretical focus or target of the intervention (25), as described below. The educational category reflects pedagogical interventions, verbal or written, with a knowledge-based emphasis designed to convey information. Strategies included one-to-one and group teaching, the use of written and audiovisual materials, mailed materials and telephone instructions. Behaviourally focused interventions were intended to change adherence by targeting, shaping or reinforcing specific behavioural patterns. These included strategies such as skill building and practice activities, behavioural modelling, packaging, dosage modifications, and both mail and telephone reminders. Affective interventions attempted to influence adherence through appeals to feelings and emotions or social relationships and social supports. These strategies included family support, counselling and supportive home visits. Provider interventions included strategies directed towards healthcare practitioners, for example educational programmes designed to help the provider improve patients' medication adherence through better instruction or communication.

### Adherence categories

For the purpose of this review, medication adherence is said to encompass both medication compliance and medication persistence. The aspect of medication adherence (compliance or persistence or both) evaluated in each study was assessed. Medication compliance is said to be measured if the study assessed administered medication doses per defined period of time, or the proportion of prescribed doses taken in a given time interval (13). Common measures of medication compliance include patient self-report, electronic monitoring, pill count and refill records. Medication persistence is said to be measured if the study assessed the duration of time from initiation to discontinuation of therapy (13). Medication persistence can be studied in terms of its duration and as a time-dependent rate (for example percentage of patients who are persistent with treatment at 6 months).

## Results

The search retrieved 26 studies that met the inclusion criteria (27–52) (Figure 1). The characteristics and outcomes of the studies are summarised in Tables 1 and 2. The majority of included studies were conducted in the United States ($n = 21$) (30,32–46,48–52), and were published within the past decade ($n = 23$) (27–32,36–52). With the exception of one study which was conducted in an outpatient psychiatric setting (45), all other studies were conducted in primary care settings. The sample size varied greatly, ranging from 45 to 1801 patients, with a mean sample size of 428 and a median sample size of 339. For studies that reported subjects' age and gender, the mean age of subjects ranged between 38 and 76 years, with the proportion of female subjects varying between 7% and 88.9%. Only eight studies (27,29–31,33,38,43,52) reported information on antidepressant treatment characteristics. Fourteen studies included patients starting antidepressant treatment (28–32,38,41,43,45,46,48,50–52), three included patients who were already receiving treatment (35,36,47), six included both types of patients (37,39,40,42,44,49) while the rest were unclear (27,33,34).

### Medication adherence assessments

In terms of the aspect of medication adherence assessed, 12 studies (46%) (29,33–36,39,40,43–46,48) examined both medication compliance and persistence, nine (35%) (27,31,32,38,42,47,50–52) medication compliance only while the remaining five studies (19%) (28,30,37,41,49) examined medication persistence only. The definition of adherence varied between studies. Studies assessing both medication compliance and persistence mainly defined adherence as the adequate dosage of antidepressants for 30 or 90 days as established by the Agency for Health Care

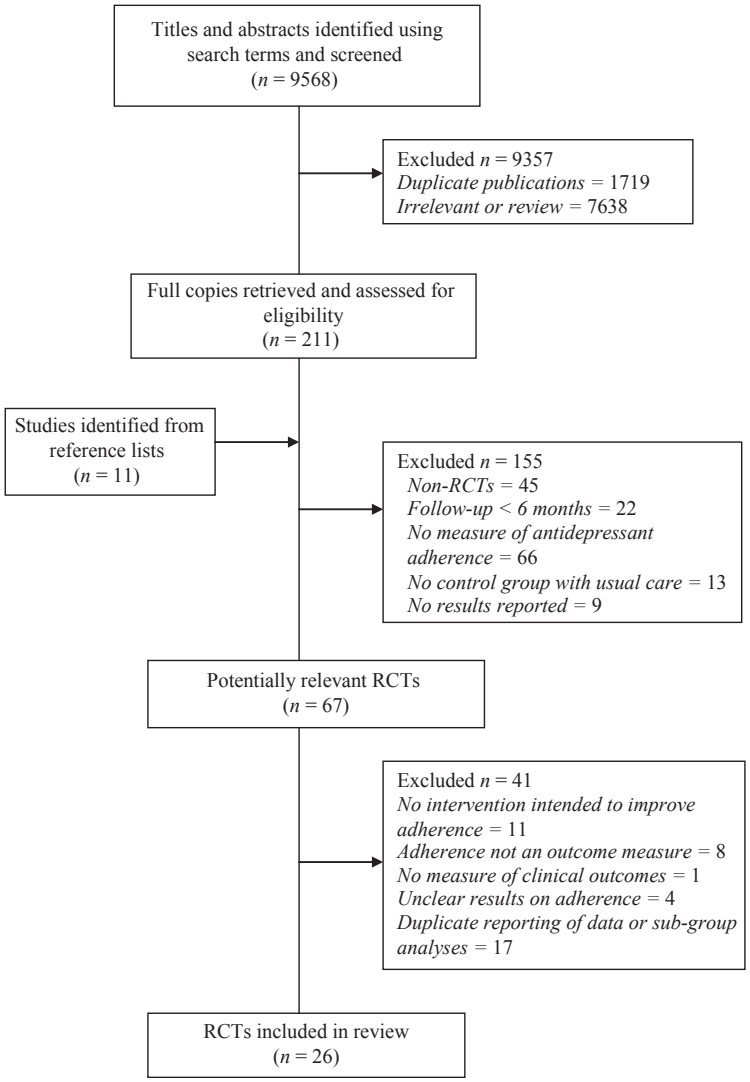


**Figure 1** Flow chart of study selection process

Policy and Research (AHCPR) depression treatment guidelines (53). The majority of studies evaluating only the compliance aspect assessed the percentage of correct medication intake or sufficient medication refills to infer at least 80% adherence during 6 months of treatment (31,32,42,50–52). Studies evaluating only the persistence aspect assessed medication persistence as a function of gap between medication refills (calculated from the intended days supply plus 10% of the total quantity prescribed from one visit to the next) (30), patients' reported use of antidepressants at follow-up (37,41,49) or collection of prescriptions in all 6 months of treatment (28).

Twenty studies (28–30,32,33,36–41,44–52) used a single adherence assessment tool while the remaining studies employed two or more different methods of adherence measurement. The most frequent method used was pharmacy records or computerised administrative databases ($n$ = 16) (28,30,31,33–36,38,40,42,43,45,46,48,51,52). This method was frequently used to assess both compliance and persistence with antidepressant medications. Other indirect adherence measures used were pill counts and electronic pill containers (29,31). Patient self-report was used in 13 studies (27,32,34,35,37,39,41–44,47,49,50).

## Methodological quality of studies

The unit of randomisation varied across studies. Eighteen studies (28–37,43,45,46,48–52) were randomised at the patient level, three studies (27,38,40) at the practitioner level and five studies (39,41,42,44,47) at the practice level. Seventeen studies (28,29,33–37,39–41,45–51) described adequate randomisation, 18 (29,32–42,44–46,48,50,52) clearly reported blinding of outcomes assessment and 19 (30,32,33,35–48,50,51) reported at least 80% patient follow-up. Sample size calculation was reported in 17 studies (28,31,33,37,39–42,44–52).

**Table 1** Interventions with an educational or behavioural focus aimed at improving antidepressant adherence in patients with unipolar depression

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/ persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/ persistence/ combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| **Educational-focused interventions** | | | | | | | | | | |
| Akerblad et al.‡ (27) | Sweden | Primary care | *N* = 1031, Age = 48.4 Women = 71.9% Unclear | 366 | 339 | Patient educational compliance enhancing programme RHYTHMS consisting of educational material on depression treatment, mailed letters and telephone follow-up | Compliance Questioning, serum levels, appointments kept and a composite index including all three methods | 1, 3 and 6 | Compliance: No significant difference between groups | Treatment response (MADRS) at week 24: Intervention > control (71.0% vs. 60.5%; p = 0.01) |
| Atherton- Naji et al. (28) | UK | Primary care | *N* = 45 Age = NS Women = 88.9% New AD users | 24 | 21 | Computer-generated educational intervention consisting of mailed information tailored to patient | Persistence General practice records | 6 | Persistence: No significant difference between groups | Mental health status (HADS) at 6 months: Intervention > control (Median score 11.0 vs. 18.0; p = 0.021) |
| Kutcher et al. (29) | Canada | Primary care | *N* = 269 Age = NS Women = NS New AD users | 131 | 138 | RHYTHMS adherence enhancement programme consisting of mailed information about depression and its pharmacological treatment | Compliance and persistence Pill counts | Weeks 1,3,5,7,9,13, 17,21,25 and 29 | Compliance: No significant difference between groups | Remission (DSM-1V /HDRS): No significant difference between groups |
| Mundt et al. (30) | USA | Primary care | *N* = 246 Age = 40.5 Women = 78.9% New AD users | 122 | 124 | Patient education programme (RHYTHMS) consisting of mailed educational materials in a time-phased manner | Persistence Prescription fill data | 1,3, and 7 | Persistence: No significant difference between groups | Depression severity (HDRS): No significant difference between groups |

 

 





**Table 1** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/ persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/ persistence/ combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Brook et al. (31) | The Netherlands | Primary care | *N* = 135<br>Age = 43<br>Women = 70%<br>New AD users | 64 | 71 | Community pharmacy-based coaching programme consisting of 3 coaching contacts, take-home videotape and written material emphasising importance of adherence | Compliance<br>Electronic pill container, pharmacy medication records | 6 | Compliance:<br>No significant difference between groups | Depressive symptoms (SCL-13):<br>No significant difference between groups |
| **Behavioural-focused intervention** | | | | | | | | | | |
| Anne Sirey et al. (32) | USA | Primary care | *N* = 70<br>Age = 76<br>Women = 77%<br>New AD users | 33 | 37 | Treatment Initiation and Participation (TIP) programme involving individual meetings and follow-up telephone calls to identify and target psychological barriers to depression treatment | Compliance<br>Patient self-report | 6 weeks<br>3, 6 months | Compliance:<br>Intervention > control ($p < 0.001$) | Depression symptoms (HDRS):<br>Intervention > control ($p < 0.01$) |

*Combined measure of adherence integrates both compliance and persistence aspects into one single measure. †Depression outcomes in studies were evaluated using various measures as stated in brackets. ‡Study evaluated two different interventions; only patient-focused intervention arm is reported herein. *N*, number of subjects; Age, mean years; AD, antidepressant; NS, Not stated; MADRS, Montgomery-Asberg Depression Rating Scale; HADS, Hospital Anxiety and Depression Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition; HDRS, Hamilton Depression Rating Scale; SCL, Hopkins Symptom Checklist Depression Scale.

**Table 2** Multifaceted interventions aimed at improving antidepressant adherence in patients with unipolar depression

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Katon et al. (33) | USA | Primary care | *N* = 217<br>Age = 47<br>Women = 76%<br>Not clear | 108 | 109 | Multifaceted intervention consisting of increased intensity and frequency of visits with a PCP and psychiatrist, patient education, continued surveillance of adherence to medication regimens and PCP training in the treatment of depression | Compliance and persistence<br>Computerised prescription refill records | 1, 4 and 7 | Combined:<br>Major depression: Intervention group > control group (75.5% vs. 50.0%; $p < 0.01$)<br>Minor depression: Intervention group > control group (79.7 vs. 40.3%; $p < 0.001$) | 50% Improvement in depression symptoms (SCL-90)<br>Major depression: Intervention group > control group (74.4 vs. 43.8%; $p < 0.01$)<br>Minor depression: No significant difference between groups |
| Katon et al. (34) | USA | Primary care | *N* = 153<br>Age = 47<br>Women = 74%<br>Not clear | 77 | 76 | Structured depression treatment programme consisting of patient and PCP education, direct and telephone contacts with psychologists, behavioural treatment to increase use of adaptive coping strategies and counselling to improve medication adherence | Compliance and persistence<br>Patient self-report by telephone interview, computerised prescription refill records | 1, 4 and 7 | Major depression: Compliance (patient self-report): 4-month: Intervention group > control group (89% vs. 62%; $p = 0.02$)<br>7-month: No significant difference between groups<br>Combined (Automated prescription data): No significant difference between groups<br>Minor depression: Compliance: 4-month: Intervention group > control group (74% vs. 44%; $p = 0.01$)<br>7-month: Intervention group > control group (65% vs. 41%; $p = 0.04$)<br>Combined: No significant difference between groups | 50% Improvement in depression symptoms (SCL-20)<br>Major depression: Intervention group > control group (70.4% vs. 42.3%; $p = 0.04$)<br>Minor depression: No significant difference between groups |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size: Intervention group | Sample size: Control group | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| Katon et al. (35) | USA | Primary care | *N* = 228<br>Age = 47<br>Women = 75%<br>Continuing AD users | 114 | 114 | Stepped collaborative care intervention targeting patients with persistent depressive symptoms; intervention consisted of enhanced education, increased frequency of visits by a psychiatrist working with the PCP and antidepressant pharmacy refill monitoring. | Compliance and persistence<br>Patient self-report, computerised pharmacy records | 1,3, and 6 | Compliance (patient self- report):<br>3-month: Intervention group > control group (78.6% vs. 62.1%; p = 0.02)<br>6-month: Intervention group > control group (73.2% vs. 50.5%; p = 0.002)<br>Combined (Automated prescription data):<br>Intervention group > control group (68.8% vs. 43.8%; p < 0.0001) | Remission (SCID):<br>3-month: Intervention group > control group (40% vs. 23%; p = 0.01)<br>6-month: Intervention group > control group (44% vs. 31%; p = 0.05) |
| Katon et al. (36) | USA | Primary care | *N* = 386<br>Age = 46<br>Women = 73.7%<br>Continuing AD users | 194 | 192 | Relapse prevention programme that included enhanced patient education, 2 visits with a depression specialist, pharmacy refill monitoring, and telephone monitoring and follow-up | Compliance and persistence<br>Computerised automated data from prescription refills | 3, 6, 9 and 12 | Combined:<br>Intervention group > control group (Odds ratio 2.08; 95% CI, 1.41-3.06; p < 0.001) | Depressive symptoms (SCL-20):<br>Intervention group > control group (Mean difference = 0.08, p = 0.04)<br>Relapse/recurrence (SCID): No significant difference between groups |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Unutzer et al. (37) | USA | Primary care | *N* = 1801<br>Age = 71.2<br>Women = 65%<br>All current users | 906 | 895 | IMPACT program (Improving Mood-Promoting Access to Collaborative Treatment) involving access to a depression care manager who provided education, care management, medication support for PCP and a brief psychotherapy for depression, Problem Solving Treatment in Primary Care | Persistence (any AD use)<br>Patient self-report | 3,6 and 12 | Persistence:<br>6 months: Intervention group > control group (68.9% vs. 52.3%; $p < 0.001$)<br>12 months: Intervention group > control group (73% vs. 57.2%; $p < 0.001$) | Treatment response (SCL-20):<br>6 months: Intervention group > control group (49.3% vs. 30.9%, $p < 0.001$)<br>12 months: Intervention group > control group (44.7% vs. 19.2%; $p < 0.001$) |
| Katzelnick et al. (38) | USA | Primary care | *N* = 407<br>Age = 45.4<br>Women = 77.5%<br>New AD users | 218 | 189 | Depression management programme (DMP) consisting of patient education materials, physician education programmes, telephone-based treatment coordination, and AD pharmacotherapy initiated and managed by primary care providers | Compliance (> 3 fills at 6 months)<br>Pharmacy refill data | 6 weeks, 3, 6, 12 months | Compliance:<br>6 months: Intervention group > control group (69.3% vs. 18.5%; $p < 0.001$) | Treatment response (HDRS):<br>12 months: Intervention > control (53.2% vs. 32.8%; $p < 0.001$) |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Wells et al. (39) | USA | Primary care | *N* = 1356<br>Age = 44<br>Women = 71%<br>All current users | 913 | 443 | Quality improvement programme (QI-meds & QI-therapy) involving institutional commitment, training local leaders to provide clinician and patient education, identification of a pool of potentially depressed patients, and either nurses for medication follow-up or access to trained psychotherapists. | Compliance and persistence<br>Patient self-report | 6 and 12 | Combined:<br>6 months: Intervention group > control group (34.7% vs. 25.1%; p = 0.001)<br>12 months: Intervention group > control group (31% vs. 24%; p = 0.01) | Probable disorder (CES-D)‡<br>6 months: Intervention group < control group (39.9% vs. 49.9%; p = 0.001)<br>12 months: Intervention group < control group (41.6% vs. 51.2%; p = 0.005) |
| Dobscha et al. (40) | USA | Primary care | *N* = 375<br>Age = 57<br>Women = 7%<br>All current users | 189 | 186 | The depression decision support team provided a single patient educational contact as well as symptom and adherence monitoring with feedback to clinicians over 12 months | Compliance and persistence<br>Computerised database | 6 and 12 | Persistence:<br>ADs for 90 days or more:<br>Intervention group > control group (76.2% vs. 61.6%; p = 0.008)<br>ADs for 180 days or more:<br>No significant difference between groups<br>Combined: Intervention group > control group (72.1% vs. 58.4%; p = 0.019) | Depression severity (SCL-20) at 6 and 12 months: No significant difference between groups |
| Dietrich et al. (41) | USA | Primary care | *N* = 405<br>Age = 42<br>Women = 80%<br>New AD users | 224 | 181 | Telephone support by care managers with feedback to clinicians and supervision from psychiatrists | Persistence (any AD use)<br>Patient self-report | 3 and 6 | Persistence:<br>No significant difference between groups | Treatment response (SCL-20) at 6 months: Intervention group > control group (59.9% vs. 46.6%; p = 0.021)<br>Remission (SCL-20) at 6 months: Intervention group > control group (37.3% vs. 26.7%; p = 0.014) |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size: Intervention group | Sample size: Control group | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| Fortney et al. (42) | USA | Primary care | *N* = 395<br>Age = 59.2<br>Women = 8%<br>All current users | 177 | 218 | Telemedicine-based collaborative care intervention consisting of scripted telephone encounters with nurse care managers, feedback to PCPs, medication management by pharmacists and psychiatric consultations with telepsychiatrists | Compliance<br>Patient self-report and pharmacy records | 6 and 12 | Compliance<br>6 months: Intervention group > control group (74.5% vs. 68.3%; p = 0.04)<br>12 months: Intervention group > control group (76.4% vs. 66.2%; p = 0.01) | Treatment response (SCL-20)<br>6 months: Intervention group > control group (23.8% vs. 15.5%; p = 0.02)<br>12 months: No significant difference between groups<br>Remission (SCL-20)<br>6 months: No significant difference between groups<br>12 months: Intervention group > control group (24.0% vs. 12.7%; p = 0.02) |
| Hunkeler et al. (43) | USA | Primary care | *N* = 302<br>Age = 55.4<br>Women = 69%<br>New AD users | I1: 117<br>I2: 62 | 123 | Intervention 1: Telehealth care consisting of emotional support and focused behavioural interventions in ten 6-min calls by primary care nurses Intervention 2: Telehealth care plus peer support consisting of telephone and in-person supportive contacts by trained health plan members recovered from depression | Compliance and persistence<br>Patient self-report, computerised pharmacy records | 6 weeks and 6 months | Compliance and persistence: No significant difference between groups | Both interventions: Depressive symptoms (50% improvement in HDRS):<br>6 months: Intervention group > control group (57% vs. 38%; p = 0.003) |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Rost et al. (44) | USA | Primary care | *N* = 479<br>Age = 42.6<br>Women = 83.9%<br>All current users | 239 | 240 | Quality Enhancement by Strategic Teaming (QUEST) intervention involving two primary care physicians, one nurse, and one administrative staff member in each intervention practice receiving brief training to improve the detection and management of major depression | Compliance and persistence<br>Patient self-report | 6 | Combined:<br>New treatment episode:<br>Intervention group > control group (36.1% vs. 9.8%; p = 0.0003)<br>Recent treatment: No significant difference between groups | Depression symptoms severity (mCES-D):<br>New treatment episode:<br>Intervention group > control group (Decrease in score 8.2, 95% CI, 0.2-16.1; p = 0.04)<br>Recent treatment:<br>No significant difference between groups |
| Simon et al. (45) | USA | Psychiatric practice | *N* = 207<br>Age = 43<br>Women = 65%<br>New AD users | 103 | 104 | Three session telephone care management program involving assessment of depressive symptoms, medication adherence and medication side-effects with structured feedback to treating psychiatrists | Compliance and persistence<br>Computerised pharmacy records | 3 and 6 | Combined:<br>No significant difference between groups | Depression severity (SCL-20):<br>6 months: No significant difference between groups |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size: Intervention group | Sample size: Control group | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| Simon et al. (46) | USA | Primary care | *N* = 600<br>Age = 44.5<br>Women = 74.3%<br>New AD users | I1: 207<br>I2:198 | 195 | Intervention 1: Telephone care management consisting of at least three outreach calls, structured feedback to the treating physician and care coordination<br>Intervention 2: Telephone care management plus psychotherapy consisting of care management integrated with a structured 8-session cognitive-behavioural psychotherapy program delivered by telephone | Compliance and persistence<br>Computerised pharmacy records | 6 weeks, 3 and 6 months | Combined<br>Intervention 1: Intervention group > control group (54% vs. 41%; p = 0.01)<br>Intervention 2: No significant difference between groups | 50% Improvement in depression symptoms (SCL) at 6 months:<br>Intervention 1: No significant difference between groups<br>Intervention 2: Intervention group > control group (58% vs. 43%; p = 0.005) |
| Gensichen et al. (47) | Germany | Primary care | *N* = 626<br>Age = 51<br>Women = 76.4%<br>Majority continuing AD users | 310 | 316 | Telephone case management by health care assistants involving structured telephone interviews to monitor depression symptoms and support medication adherence, with feedback to the family physicians | Compliance<br>Modified Morisky patient self-report scale | 6 and 12 | Compliance<br>12-month: Intervention group > control group (mean score 2.70 vs. 2.53; p = 0.042) | Depression symptoms (PHQ-9):<br>12-month: Intervention group > control group (mean score 10.7 vs. 12.1; p = 0.014) |
| Simon et al.[§] (48) | USA | Primary care | *N* = 613<br>Age = 46.5<br>Women = 72%<br>New AD users | 196 | 196 | Feedback plus care management involving systematic follow-up by telephone, sophisticated treatment recommendations and practice support by a care manager | Compliance and persistence<br>Computerised pharmacy data | 3 and 6 | Combined: Intervention group > control group (moderate adequate dose for ≥ 90 days) (30% vs. 18%; p < 0.05) | 50% Improvement in depression symptoms: (SCL-20)<br>Intervention group > control group (56% vs. 40%; p < 0.05) |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Adler et al. (49) | USA | Primary care | *N* = 507<br>Age = 42.3<br>Women = 71.8%<br>All current users | 258 | 249 | Pharmacist intervention involving medication review and monitoring by pharmacists, patient contact and education, general social support and providing feedback to PCPs | Persistence<br>Patient self-report | 3 and 6 | Persistence at 6 months:<br>Intervention group > control group (57.5% vs. 46.2%; p = 0.025) | Depression severity (mBDI):<br>No significant difference between groups |
| Capoccia et al. (50) | USA | Primary care | *N* = 74<br>Age = 39<br>Women = 77%<br>New AD users | 41 | 33 | Pharmacist collaborative care intervention consisting of additional phone follow-up by pharmacists; phone contacts focused on support, patient education and medication management | Compliance<br>Self-reported telephone interview | 3, 6, 9 and 12 | Compliance<br>No significant difference between groups | Depression symptoms (SCL-20):<br>No significant difference between groups |
| Rickles et al. (51) | USA | Community pharmacies | *N* = 63<br>Age = 38<br>Women = 84%<br>New AD users | 31 | 32 | Pharmacist-guided education and monitoring (PGEM) involving three monthly telephone calls to patients to assess, monitor and make recommendations to improve patient's medication adherence | Compliance<br>Pharmacy records | 3 and 6 | Compliance<br>No significant difference between groups | 50% Improvement in depression symptoms (BDI- II):<br>No significant difference between groups |

 

**Table 2** (Continued)

| Study | Country | Setting | Subject characteristics Patient population (new or continuing AD users) | Sample size | | Description of experimental intervention | Aspect of adherence assessed (compliance/persistence/both) Methods used to assess adherence | Follow-up times (months) | Adherence (compliance/persistence/combined*) outcomes (intervention vs. control group) | Depression outcomes† (intervention vs. control group) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Intervention group | Control group | | | | | |
| Finley et al. (52) | USA | Primary care | *N* = 125<br>Age = 54<br>Women = 85%<br>New AD users | 75 | 50 | Pharmacist collaborative care intervention consisting of patient education, frequent follow-up contacts through telephone calls and clinic appointments, medication management by clinical pharmacists; recommendation to providers and supervision of pharmacists by a psychiatrist | Compliance<br>Computerised prescription refill records | 3 and 6 | Compliance<br>6 months:<br>Intervention group > control group (67% vs. 48%; p = 0.038) | Depression symptoms (BIDS): No significant difference between groups |

*Combined measure of adherence integrates both compliance and persistence aspects into one single measure. †Depression outcomes were evaluated using various measures as stated in brackets. ‡Intervention significantly reduced the percentage of patients with probable depression at 6 and 12 months. §Study evaluated two different interventions; only patient-focused intervention arm is reported herein. *N*, number of subjects; Age, mean years; AD, antidepressant; PCP, primary care physician; SCL, Hopkins Symptom Checklist Depression Scale; SCID, Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition;* HDRS, Hamilton Depression Rating Scale; CES-D, Center for Epidemiologic Studies Depression Scale; PHQ, Patient Health Questionnaire; BDI, Beck Depression Inventory; BIDS, Brief Inventory for Depressive Symptoms.

## Effectiveness of intervention strategies

*Educational focus*

As shown in Table 1, five studies (27–31) utilised interventions with an educational focus. Four (27–30) of these used mailed educational materials whereas one (31) used verbal counselling by pharmacists in addition to written materials and video. Three (27,29,30) interventions used the RHYTHMS programme, a patient education programme which mails information directly to patients being treated with antidepressant medications in a time-phased manner. None of the educational intervention studies reported an improvement in medication compliance or persistence, although two studies (27,28) reported improvement in treatment response and mental health status at 6 months follow-up.

*Behavioural focus*

Only one study (32) in this review utilised an intervention with a behavioural focus. The study involved a novel psychosocial intervention aimed at identifying and addressing psychological barriers, fears and misconceptions of depression treatment. This intervention resulted in improvement of both medication compliance and depressive symptoms.

*Multifaceted interventions*

*Components of multifaceted interventions.* A majority of interventions employed more than a single component strategy (educational, behavioural or affective) and targeted both the patient and the healthcare provider. Overall, 20 studies (33–52) reported utilising multifaceted interventions (Table 2). Two of the studies (43,46) reported two multifaceted interventions each, bringing the total number of multifaceted interventions in this review to 22.

The individual components of multifaceted interventions were grouped into educational, behavioural, affective and provider-targeted strategies (Table 3). Care management or patient follow-up was the central theme in most of the multifaceted interventions tested. In 14 studies (36,37,39–45,47,49–52), the care managers were allied health professionals. Eleven studies (34,36,37,39,41,43–47,49) described training for care managers which included workshops, training manuals, didactic instruction and observed care manager contacts.

It is clear from Table 3 that some components were more frequently used than others. For example, patient education was most commonly conducted through written and audiovisual materials. As for behavioural strategies, commonly employed strategies were patient follow-up through telephone or scheduled clinic appointments, development of a behavioural or relapse prevention plan and pharmacy refill monitoring. All seven interventions (33–36,38,40,48) that employed pharmacy refill monitoring reported an improvement in antidepressant adherence. Twelve interventions (34,36,37,41,43,44,46,48–50) reported using affective strategies such as providing emotional or general social support and motivational interviewing techniques. All of the multifaceted studies utilised some form of provider-targeted strategy, with the majority using strategies such as providing feedback and medication support to the primary care provider.

*Effectiveness of multifaceted interventions.* Of the 22 multifaceted interventions tested, 11 (33–39,42,44,47,48) reported positive effects for both medication adherence and depression outcomes relative to the usual care group. Four interventions (40,46,49,52) reported positive effects for medication adherence outcomes only, four (41,43,46) improved depression outcomes without improving medication adherence and three (45,50,51) failed to demonstrate improvement for both types of outcomes.

Several multifaceted interventions involved collaborative care between primary care physicians and the mental health speciality sector (33–35,37). Psychiatrists and psychologists were integrated into the primary care, whereby their roles included providing medication support to the primary care providers (PCPs) through treatment recommendations and consultations, providing brief psychotherapy or supervision of care management. Two studies by Katon and colleagues (33,34) in the mid-1990s showed that such collaborative care together with enhanced patient education, training of PCPs and continued surveillance of medication adherence improved medication adherence outcomes (compliance and persistence). However, the clinical outcomes were improved only in patients with major depression. In separate studies, the authors targeted collaborative care in difficult-to-treat patients and found that collaborative care significantly improved medication adherence (compliance/persistence) and depression outcomes in patients with persistent depressive symptoms (35) as well as those with high risk of relapse or recurrence (36). The IMPACT (Improving Mood-Promoting Access to Collaborative Treatment) study (37) demonstrated the value of the collaborative care model in late-life depression, both in terms of antidepressant adherence and depression outcomes.

**Table 3** Summary of multifaceted intervention components utilised by interventions

| Strategies | Frequency (*N*) | Percentage (%) | Reference |
|---|---|---|---|
| **Care management function:** | | | |
| Discipline: | | | |
| Psychiatrists or psychologists | 4 | 20 | (33–35,46) |
| Clinical pharmacists | 4 | 20 | (49–52) |
| Nurses | 6 | 30 | (39,40,42–45) |
| Mixed: Psychologists, nurses and social workers | 3 | 15 | (36,37,41) |
| Healthcare assistants | 1 | 5 | (47) |
| Non-clinicians | 2 | 10 | (38,48) |
| Special training required: | | | |
| Yes | 11 | 55 | (34,36,37,39,41,43–47,49) |
| No/not stated | 9 | 45 | (33,35,38,40,42,48,50–52) |
| **Educational strategies** | | | |
| Oral | 9 | 40.9 | (33–35,37,39,40,44,49,52) |
| Written/audiovisual | 10 | 45.5 | (33–39,44,46,49) |
| Telephone education | 4 | 18.2 | (42,49–51) |
| Mailed materials | 2 | 9.1 | (40,42) |
| **Behavioural strategies** | | | |
| Telephone follow-up/monitoring | 18 | 81.8 | (34,36–38,41–52) |
| Scheduled clinic visits | 9 | 40.9 | (33–39,44,52) |
| Development of behavioural or relapse prevention plan | 10 | 45.5 | (34,36,37,39,43,44,46,47) |
| Psychotherapy | 4 | 18.2 | (34,37,39,46) |
| Pharmacy refill monitoring | 7 | 31.8 | (33–36,38,40,48) |
| Mail reminders | 4 | 18.2 | (36,45,46) |
| Telephone reminders | 3 | 13.6 | (35,36,48) |
| **Affective strategies** | | | |
| Emotional/social support | 9 | 40.9 | (34,37,41,43,44,48–50) |
| Motivational interviewing techniques | 3 | 13.6 | (36,46,49) |
| **Provider-targeted strategies** | | | |
| PCP education | 9 | 40.9 | (33,34,38–42,44,47) |
| Medication support (treatment algorithm/expert advice) | 16 | 72.2 | (33–35,37–42,44–46,48,49,52) |
| Feedback to PCP on patient progress | 18 | 81.8 | (33–36,38–49) |
| Medication review and management by pharmacist | 5 | 22.7 | (42,49–52) |
| Facilitation of referrals to mental health sector | 8 | 36.4 | (35,40,45,46,48–50) |
| Physician reminders/alerts on non-adherence | 3 | 13.6 | (33,35,36) |
| Supervision from specialist psychiatric services | 17 | 77.3 | (33–35,37,38,40–43,45,46,48–50,52) |

Other intensive depression care programmes have also shown positive results. A depression management programme was found to significantly improve both medication compliance and depression outcomes in high utilisers of medical services who were identified to be depressed but were not receiving active treatment (38). In another study, quality improvement was targeted at improving adherence to either appropriate antidepressant medication or cognitive-behavioural therapy (39). This complex intervention which involved several key elements resulted in significant improvements in both medication adherence (compliance/persistence) and depression outcomes. In contrast, a lower intensity intervention consisting mainly of monitoring patient's progress and providing the resultant feedback to treating clinicians resulted in enhanced short-term medication persistence, but not long-term persistence or depression outcomes (40).

Telephone-based care management was the focus of several multifaceted studies. In five studies (41–45), the care managers were registered nurses who monitored depressive symptoms, medication adherence and medication side-effects. They provided feedback on the progress of patients to doctors after each telephone contact. In one study (43), the nurses also provided emotional support and helped patients develop behavioural plans. Of the five studies with nurses as care managers, two (42,44) demonstrated improvement in medication adherence (compliance and persistence) and clinical outcomes. In the only study to report an intervention in psychiatric practice (45), telephone-based care management by nurses did not improve antidepressant adherence

(compliance/persistence) or depression outcomes. Other studies have employed mental health clinicians (46), healthcare assistants (47) and non-clinicians (48) as telephone-based care managers with resulting improvement in medication adherence (compliance and persistence) outcomes.

Pharmacist-based interventions were used in four studies (49–52). The interventions involved pharmacists providing patient education, as well as reviewing and managing patients' antidepressant medication regimen. In three of the studies (49,50,52), the pharmacists collaborated with PCPs by providing feedback on patients' progress and treatment recommendations. Pharmacists also performed care management functions by monitoring patients' medication adherence through telephone follow-up, facilitating referrals to mental health speciality sectors as well as providing general social support. In two of the pharmacy-based interventions (49,52), antidepressant medication persistence and compliance each improved although none of the interventions resulted in improvement of depression outcomes.

## Discussion

Our findings indicate some evidence for improvement in both antidepressant medication compliance and persistence through multifaceted interventions that employed combinations of educational, behavioural, affective and provider-targeted strategies. This is in line with previous reviews (21–23,54), and reflects the multifactorial nature of medication adherence problems. It also highlights the need to target all dimensions affecting medication adherence problems – the patient, the healthcare provider and the health care delivery system. This need is also supported by the results of previous studies which have reported the failure of interventions targeting healthcare providers only (55,56). Our findings add to the literature with regard to the different aspects of medication adherence (compliance or persistence) assessed in intervention studies, as well as the key components used in multifaceted interventions seeking to improve antidepressant adherence.

About two-thirds of multifaceted interventions in this review reported improving antidepressant adherence outcomes, whereas half reported improving both adherence and depression outcomes. Generally, those that were most successful in improving both adherence and clinical outcomes were those with a larger number of elements involved and/or more intensive patient care monitoring. Given the nature of depression as an episodic and chronic illness, it is likely that more intensive patient monitoring such as higher frequency of follow-up sessions and longer duration of intervention, has a higher impact on outcomes. Frequent follow-up sessions may be necessary not only to reinforce benefits of the intervention, but also to foster therapeutic alliance between healthcare providers and patients. In addition, multifaceted interventions that integrated mental health specialists into primary care settings were also successful in improving both antidepressant adherence and depression outcomes (33–35,37,38). However, these interventions may not always be feasible, given that most primary care practices do not have on-site mental health specialists. Thus, the potential roles of allied healthcare professionals such as nurses, pharmacists, healthcare assistants and social workers in improving depression management are of particular interest. Studies in this review have shown that these allied healthcare professionals can be instrumental in helping improve patient adherence outcomes in depression through care management, patient education and medication support activities (37,39,40,42,44,47,49,52). We also observed that interventions producing improvements in adherence and clinical outcomes tended to involve active collaboration and coordination between the allied healthcare professionals, mental health specialists and PCPs. Further research should thus explore the most appropriate ways to promote collaborative care among healthcare practitioners, and to integrate the skills of these practitioners into an effective model of treatment delivery for depression.

The value of patient-provider collaboration was in turn reflected by the favourable outcomes of the Treatment Initiation and Participation Program (TIP), the only intervention in this review to utilise a behavioural-focused strategy (32). This novel psychosocial intervention, which was designed to focus on collaboration to empower the patient to self-manage his or her medication treatment showed positive results on both adherence and clinical outcomes. Although the relatively small sample size of older adult patients with late-life depression raises the issue of generalisability to other patient populations, the promising results of this study suggest the importance of the therapeutic alliance factor in improving antidepressant adherence. In their review, Lingam and Scott also highlighted the role of establishing a 'good' doctor–patient relationship in improving adherence (18). Studies in mental health have also suggested the potential benefits of shared decision-making between clinicians and patients in developing treatment plans (57–60).

Interventions relying solely on educational strategies failed to demonstrate any improvement in medication adherence, specifically compliance and persistence in patients starting antidepressant treat-

ment. This was despite the interventions being time-phased and tailored to the patient's stage of treatment (27–30). The interventions did, however, report improving other aspects of patient care such as satisfaction with treatment (29) and patients' attitude to antidepressant medications (61). One possible reason for the lack of effectiveness of these educational interventions could be the impersonal nature of the interventions themselves, which comprised mainly of mailed materials. Also, the methods used to measure adherence levels in some of the studies such as pill counts and electronic monitoring could have posed an independent intervention effect as patients were aware that their adherence was being closely monitored (29,31).

In the current review, a few studies reported an improvement in clinical outcomes but not on adherence outcomes (27,28,41,43). Although adherence to therapy has been shown to improve clinical outcomes (62), medication-taking behaviour is not the only factor influencing clinical outcomes. This may be especially true in the case of depressive disorders, whereby other factors likely to have an impact include patients' self-management strategies, stigma and other psychosocial issues (63,64). It may be possible that some of the multifaceted interventions addressed these other factors and therefore had a direct therapeutic benefit that was not mediated through improved medication adherence. Furthermore, the standard of care received by the control group is different between studies; it may also well differ within some studies themselves. This may have an impact on both clinical and adherence outcome measures in the control group, which ultimately may have contributed to the observed intervention effects.

Although our review found some evidence for multifaceted interventions, the challenge remained as to identifying the active elements that contributed to the success or failure of the interventions. Despite recommendations from previous reviews and studies (21,22,44) for better designed multifaceted trials, few studies reported the implementation adherence rate of the intervention and fewer reported the process of care that was involved in the implementation. Such documentation is important, as it will allow researchers and clinicians to better understand the relationship between individual components of the multifaceted interventions and outcomes. It will also allow researchers to assess whether or not such interventions are sustainable in the long run. For example, Adler and colleagues (49,65) documented all pharmacists' activities in their attempt to identify the 'active ingredients' in their pharmacist collaborative intervention. They discovered that the intervention protocol described only a minor part of what actually took place during the intervention; instead pharmacists spent a considerable time providing psychosocial support and assisting patients with obtaining care (65). In addition, although most researchers advocate the use of theoretical frameworks in developing interventions to reduce non-adherence, studies in this review are mostly empirically driven. Only a minority (28,32,34,36,37,47,51) mentioned the use of any theoretical frameworks in designing interventions.

With the exception of the study by Gensichen and colleagues (47) in Germany, all of the other multifaceted studies were conducted in the United States, and mostly in academic or highly structured settings such as health maintenance organisations. This raises the issue of the generalisability of such intervention models to different patient populations and practice settings (66). It could also be argued that the effectiveness of these interventions are related to the health care structure in which they were implemented; that the organisation of the health care delivery itself played an important role in facilitating and underpinning the success of these multifaceted interventions. More evidence is needed on the cost-effectiveness of such interventions in smaller clinic settings and other less integrated systems of care found in most countries. However, the encouraging results of the study in Germany (47), as well as some effectiveness trials conducted in diverse practice settings (37,39,44) suggested the broad potential applicability and effectiveness of the collaborative care model.

One interesting finding from this review was that interventions may need to be targeted to the different phases of antidepressant treatment. While some interventions such as the Katon models (33–36) reported improving medication adherence in the acute phase, as well as continuation and maintenance phases of treatment, other interventions appeared to be beneficial for patients in the acute phase of treatment only (44,49). However, as studies did not discuss in detail the therapeutic actions that were undertaken (such as adjustments in dosage or changes in antidepressant treatment), it was not possible for us to evaluate the effects of such actions on patients' antidepressant adherence. In addition, it may also be necessary to tailor the interventions according to the patient population. For example, the only study in this review that was conducted in a psychiatric setting failed to show any improvement using a collaborative care intervention (45). One potential reason for this may have been that the patient population in speciality care differs from that of primary care (67); patients treated by psychiatrists may have more persistent or treatment-resistant depression (45). It is possible that these patients may

require more proactive monitoring and assistance with self-management activities compared with patients newly diagnosed with depression or treatment-naive patients.

We also found that the terminology and definitions used to characterise problems with medication adherence in depression varied considerably. This lack of standardisation is a common and well-documented problem in adherence research, and there is still debate on the appropriate terminologies to describe patients' medication-taking behaviour. There is a need for a standardised taxonomy that clearly defines the concept of medication adherence to allow for comparisons among adherence interventions. Further research on a new taxonomy to address this important issue is currently underway (68). As previous studies have found that both adequate dosage and therapy length are important in the treatment of depression (69,70), it seems warranted that a clinically meaningful definition of medication adherence would encompass both aspects. Thus, it would be ideal for both compliance and persistence aspects of medication-taking behaviour to be assessed and reported in future studies seeking to improve antidepressant adherence. In this current review, it was sometimes unclear to us which aspect of adherence (compliance or persistence or both) was considered as the evaluation measure in the studies reviewed. As an example, there was uncertainty in the definition of non-persistence used by some authors (30) and whether or not this definition (function of gap between medication refills) accurately reflects medication persistence. Thus, it would be valuable for researchers to be explicit about the definition and operation of adherence measures used in their studies to allow readers to assess the aspect of adherence that is being measured.

In addition, the variety of adherence measurement tools used reflects the absence of a 'gold standard' in measuring medication adherence. It is interesting to note that although electronic monitoring has been considered to be the most accurate and informative method in assessing medication adherence (71), only one study in this review has utilised this method in measuring adherence (31). Majority of the studies utilised computerised administrative databases or pharmacy refill records to obtain adherence information. Although this method does offer a more practical and less intrusive way to assess and monitor adherence, it does have its own limitations including the inability to determine if the patient actually consumed the dispensed medicine in the expected manner (72). Still, previous researches have found high rates of agreement between self-reported antidepressant use and prescription fill data from a pharmacy database (34,43,73,74). Depending on the completeness of data, pharmacy refill records can present a useful source of information to assess medication compliance and persistence in an authentic practice setting (72,75). However, as there is no ideal method currently available in measuring medication adherence, it is recommended to use combinations of measurement tools to allow a more accurate assessment of the different aspects of medication adherence.

There are several limitations in our review. We excluded non-English publications and publications before 1990, which could have led to language and publication bias. The heterogeneity of the studies, interventions and outcome measures prevented us from comparing results between studies directly by means of meta-analysis. In addition, we broadly categorised prominent intervention components into educational, behavioural, affective and provider-targeted strategies. We acknowledge that in some intervention strategies, these components do overlap. For example, behavioural strategies such as telephone follow-up and scheduled visits may have an educational or affective component embedded in the intervention that were not necessarily reported in the research studies. This review also does not provide any perspective on the duration of the effect of the intervention after it has been completed, as only a minority of studies assessed whether or not the effect of the intervention was sustained in the long-term.

In conclusion, interventions that were successful in improving both adherence and clinical outcomes in depression were multifaceted and mostly complex, with proactive care management and involvement of mental health specialists. Given the nature of depression as a chronic and recurrent illness, ongoing supportive services may be necessary especially at critical points of treatment. It may also be necessary to tailor interventions to specific phases of antidepressant treatment (acute vs. continuation and maintenance) as well as different treatment settings (primary vs. psychiatric care). Future research seeking to improve antidepressant adherence should take into account both the compliance and persistence aspects of adherence. Trials should also document and report the process of care that was involved, especially for multifaceted interventions. Given the importance of antidepressant adherence, more rigorous and well-conducted studies are needed to improve antidepressant compliance and persistence in a variety of patient populations and settings.

## Acknowledgements

None.

## Author contributions

Wei Wen Chong designed the review, conducted the literature search, carried out data analysis/interpretation and drafted this article. Parisa Aslani and Timothy F Chen contributed in designing the review, data analysis/interpretation and in critically reviewing the manuscript.

## References


1 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349**: 1498–504.

2 Katon W, Schulberg H. Epidemiology of depression in primary care. *Gen Hosp Psychiatry* 1992; **14**: 237–47.

3 Simon GE. Evidence review: efficacy and effectiveness of antidepressant treatment in primary care. *Gen Hosp Psychiatry* 2002; **24**: 213–24.

4 World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization, 2003.

5 Sackett DL, Haynes BR. *Compliance with Therapeutic Regimens*. Baltimore, MD: John Hopkins University Press, 1976.

6 Anderson IM, Ferrier IN, Baldwin RC et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2008; **22**: 343–96.

7 National Institute for Health and Clinical Excellence. *Depression: The Treatment and Management of Depression in Adults*. http://www.nice.org.uk/CG90 (accessed November 2010).

8 American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, Third Edition. http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx. (accessed November 2010).

9 Lin EH, Von Korff M, Katon W et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care* 1995; **33**: 67–74.

10 Geddes JR, Carney SM, Davies C et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003; **361**: 653–61.

11 Melfi CA, Chawla AJ, Croghan TW et al. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psychiatry* 1998; **55**: 1128–32.

12 Cantrell CR, Eaddy MT, Shah MB et al. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Med Care* 2006; **44**: 300–3.

13 Cramer JA, Roy A, Burrell A et al. Medication compliance and persistence: terminology and definitions. *Value Health* 2008; **11**: 44–7.

14 Demyttenaere K, Mesters P, Boulanger B et al. Adherence to treatment regimen in depressed patients treated with amitriptyline or fluoxetine. *J Affect Disord* 2001; **65**: 243–52.

15 Becker MH. The health belief model and personal health behavior. *Health Educ Monogr* 1974; **2**: 324–473.

16 Azjen I. The theory of planned behaviour. *Organ Behav Hum Decis Process* 1991; **50**: 179–211.

17 Prochaska JO, DiClemente CC. Stages and processes of self-change of smoking: toward an integrative model of change. *J Consult Clin Psychol* 1983; **51**: 390–5.

18 Lingam R, Scott J. Treatment non-adherence in affective disorders. *Acta Psychiatr Scand* 2002; **105**: 164–72.

19 Keller MB, Hirschfeld RM, Demyttenaere K, Baldwin DS. Optimizing outcomes in depression: focus on antidepressant compliance. *Int Clin Psychopharmacol* 2002; **17**: 265–71.

20 Demyttenaere K. Risk factors and predictors of compliance in depression. *Eur Neuropsychopharmacol* 2003; **13**: S69–75.

21 Vergouwen ACM, Bakker A, Katon WJ et al. Improving adherence to antidepressants: a systematic review of interventions. *J Clin Psychiatry* 2003; **64**: 1415–20.

22 Pampallona S, Bollini P, Tibaldi G et al. Patient adherence in the treatment of depression. *Br J Psychiatry* 2002; **180**: 104–9.

23 Williams JW Jr, Gerrity M, Holsinger T et al. Systematic review of multifaceted interventions to improve depression care. *Gen Hosp Psychiatry* 2007; **29**: 91–116.

24 Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12.

25 Roter DL, Hall JA, Merisca R et al. Effectiveness of interventions to improve patient compliance: a meta-analysis. *Med Care* 1998; **36**: 1138–61.

26 Dolder CR, Lacro JP, Leckband S, Jeste DV. Interventions to improve antipsychotic medication adherence: review of recent literature. *J Clin Psychopharmacol* 2003; **23**: 389–99.

27 Akerblad AC, Bengtsson F, Ekselius L, von Knorring L. Effects of an educational compliance enhancement programme and therapeutic drug monitoring on treatment adherence in depressed patients managed by general practitioners. *Int Clin Psychopharmacol* 2003; **18**: 347–54.

28 Atherton-Naji A, Hamilton R, Riddle W, Naji S. Improving adherence to antidepressant drug treatment in primary care: a feasibility study for a randomized controlled trial of educational intervention. *Prim Care Psychiatr* 2001; **7**: 61–7.

29 Kutcher S, Leblanc J, Maclaren C, Hadrava V. A randomized trial of a specific adherence enhancement program in sertraline-treated adults with major depressive disorder in a primary care setting. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26**: 591–6.

30 Mundt JC, Clarke GN, Burroughs D et al. Effectiveness of antidepressant pharmacotherapy: the impact of medication compliance and patient education. *Depress Anxiety* 2001; **13**: 1–10.

31 Brook OH, van Hout H, Stalman W et al. A pharmacy-based coaching program to improve adherence to antidepressant treatment among primary care patients. *Psychiatr Serv* 2005; **56**: 487–9.

32 Anne Sirey J, Bruce ML, Kales HC. Improving antidepressant adherence and depression outcomes in primary care: the treatment initiation and participation (TIP) program. *Am J Geriatr Psychiatry* 2010; **18**: 554–62.

33 Katon W, Von Korff M, Lin E et al. Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *JAMA* 1995; **273**: 1026–31.

34 Katon W, Robinson P, Von Korff M et al. A multifaceted intervention to improve treatment of depression in primary care. *Arch Gen Psychiatry* 1996; **53**: 924–32.

35 Katon W, Von Korff M, Lin E et al. Stepped collaborative care for primary care patients with persistent symptoms of depression: a randomized trial. *Arch Gen Psychiatry* 1999; **56**: 1109–15.

36 Katon W, Rutter C, Ludman EJ et al. A randomized trial of relapse prevention of depression in primary care. *Arch Gen Psychiatry* 2001; **58**: 241–7.

37 Unutzer J, Katon W, Callahan CM et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002; **288**: 2836–45.

38 Katzelnick DJ, Simon GE, Pearson SD et al. Randomized trial of a depression management program in high utilizers of medical care. *Arch Fam Med* 2000; **9**: 345–51.

39 Wells KB, Sherbourne C, Schoenbaum M et al. Impact of disseminating quality improvement programs for depression in managed primary care: a randomized controlled trial. *JAMA* 2000; **283**: 212–20.

40 Dobscha SK, Corson K, Hickam DH et al. Depression decision support in primary care: a cluster randomized trial. *Ann Intern Med* 2006; **145**: 477–87.

41 Dietrich AJ, Oxman TE, Williams JW Jr et al. Reengineering systems for the treatment of depression in primary care: cluster randomised controlled trial. *BMJ* 2004; **329**: 602–5.

42 Fortney JC, Pyne JM, Edlund MJ et al. A randomized trial of telemedicine-based collaborative care for depression. *J Gen Intern Med* 2007; **22**: 1086–93.

43 Hunkeler EM, Meresman JF, Hargreaves WA et al. Efficacy of nurse telehealth care and peer support in augmenting treatment of depression in primary care. *Arch Fam Med* 2000; **9**: 700–8.

44 Rost K, Nutting P, Smith J et al. Improving depression outcomes in community primary care practice: a randomized trial of the quEST intervention. Quality Enhancement by Strategic Teaming. *J Gen Intern Med* 2001; **16**: 143–9.

45 Simon GE, Ludman EJ, Operskalski BH. Randomized trial of a telephone care management program for outpatients starting antidepressant treatment. *Psychiatr Serv* 2006; **57**: 1441–5.

46 Simon GE, Ludman EJ, Tutty S et al. Telephone psychotherapy and telephone care management for primary care patients starting antidepressant treatment: a randomized controlled trial. *JAMA* 2004; **292**: 935–42.

47 Gensichen J, von Korff M, Peitz M et al. Case management for depression by health care assistants in

small primary care practices: a cluster randomized trial. *Ann Intern Med* 2009; **151**: 369–78.
48 Simon GE, VonKorff M, Rutter C, Wagner E. Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. *BMJ* 2000; **320**: 550–4.
49 Adler DA, Bungay KM, Wilson IB et al. The impact of a pharmacist intervention on 6-month outcomes in depressed primary care patients. *Gen Hosp Psychiatry* 2004; **26**: 199–209.
50 Capoccia KL, Boudreau DM, Blough DK et al. Randomized trial of pharmacist interventions to improve depression care and outcomes in primary care. *Am J Health Syst Pharm* 2004; **61**: 364–72.
51 Rickles NM, Svarstad BL, Statz-Paynter JL et al. Pharmacist telemonitoring of antidepressant use: effects on pharmacist-patient collaboration. *J Am Pharm Assoc* 2005; **45**: 344–53.
52 Finley PR, Rens HR, Pont JT et al. Impact of a collaborative care model on depression in a primary care setting: a randomized controlled trial. *Pharmacotherapy* 2003; **23**: 1175–85.
53 Depression Guideline Panel. *Clinical Practice Guideline Number 5: Depression in Primary Care, Volume 2: Treatment of Major Depression*. Rockville, MD: US Department of Health and Human Services, Agency for Health Care Policy and Research, 1993. Report No.: AHCPR Publication 93-0550.
54 Gilbody S, Whitty P, Grimshaw J, Thomas R. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *JAMA* 2003; **289**: 3145–51.
55 Lin EH, Katon WJ, Simon GE et al. Achieving guidelines for the treatment of depression in primary care: is physician education enough? *Med Care* 1997; **35**: 831–42.
56 Thompson C, Kinmonth AL, Stevens L et al. Effects of a clinical-practice guideline and practice-based education on detection and outcome of depression in primary care: Hampshire Depression Project randomised controlled trial. *Lancet* 2000; **355**: 185–91.
57 Bull SA, Hu XH, Hunkeler EM et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. *JAMA* 2002; **288**: 1403–9.
58 Bultman DC, Svarstad BL. Effects of physician communication style on client medication beliefs and adherence with antidepressant treatment. *Patient Educ Couns* 2000; **40**: 173–85.
59 Loh A, Leonhart R, Wills CE et al. The impact of patient participation on adherence and clinical outcome in primary care of depression. *Patient Educ Couns* 2007; **65**: 69–78.
60 Clever SL, Ford DE, Rubenstein LV et al. Primary care patients' involvement in decision-making is associated with improvement in depression. *Med Care* 2006; **44**: 398–405.
61 Brook O, van Hout H, Nieuwenhuyse H, Heerdink E. Impact of coaching by community pharmacists on drug attitude of depressive primary care patients and acceptability to patients; a randomized controlled trial. *Eur Neuropsychopharmacol* 2003; **13**: 1–9.
62 Akerblad AC, Bengtsson F, von Knorring L, Ekselius L. Response, remission and relapse in relation to adherence in primary care treatment of depression: a 2-year outcome study. *Int Clin Psychopharmacol* 2006; **21**: 117–24.
63 Bosworth HB, Voils CI, Potter GG, Steffens DC. The effects of antidepressant medication adherence as well as psychosocial and clinical factors on depression outcome among older adults. *Int J Geriatr Psychiatry* 2008; **23**: 129–34.
64 O'Reilly CL, Bell JS, Chen TF. Mental health consumers and caregivers as instructors for health professional students: a qualitative study. *Soc Psychiatry Psychiatr Epidemiol* 2011; doi:10.1007/s00127-011-0364-x.
65 Bungay KM, Adler DA, Rogers WH et al. Description of a clinical pharmacist intervention administered to primary care patients with depression. *Gen Hosp Psychiatry* 2004; **26**: 210–8.
66 Gilbody S, Bower P, Fletcher J et al. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med* 2006; **166**: 2314–21.
67 Cooper-Patrick L, Crum RM, Ford DE. Characteristics of patients with major depression who received care in general medical and specialty mental health settings. *Med Care* 1994; **32**: 15–24.
68 ABC Project. *Ascertaining Barriers for Compliance: policies for safe, effective and cost-effective use of medicines in Europe*. http://www.ABCproject.eu (accessed April 2011).
69 Katon W, von Korff M, Lin E et al. Adequacy and duration of antidepressant treatment in primary care. *Med Care* 1992; **30**: 67–76.
70 Donoghue J, Hylan TR. Antidepressant use in clinical practice: efficacy vs. effectiveness. *Br J Psychiatry Suppl* 2001; **42**(Suppl.): s9–17.
71 George CF, Peveler RC, Heiliger S, Thompson C. Compliance with tricyclic antidepressants: the value of four different methods of assessment. *Br J Clin Pharmacol* 2000; **50**: 166–71.
72 Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006; **15**: 565–74.
73 Saunders K, Simon G, Bush T, Grothaus L. Assessing the feasibility of using computerized pharmacy refill data to monitor antidepressant treatment on a population basis: a comparison of automated and self-report data. *J Clin Epidemiol* 1998; **51**: 883–90.
74 Kwon A, Bungay KM, Pei Y et al. Antidepressant use: concordance between self-report and claims records. *Med Care* 2003; **41**: 368–74.
75 Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997; **50**: 105–16.

## Appendix 1

Search strategy to identify interventions in MEDLINE:

| | |
|---|---|
| 1 | exp Patient Compliance/ |
| 2 | exp Medication Adherence/ |
| 3 | compliance.ti,ab. |
| 4 | (non adj compliance).ti,ab. |
| 5 | adherence.ti,ab. |
| 6 | (non adj adherence).ti,ab. |
| 7 | persistence.mp. |
| 8 | concordance.mp. |
| 9 | exp Patient Dropouts/ |
| 10 | discontinuation.mp. |
| 11 | continuity.mp. |
| 12 | exp Treatment Refusal/ |
| 13 | termination.mp. |
| 14 | exp Patient Education as Topic/ |
| 15 | or/1-14 |
| 16 | exp Depression/ |
| 17 | exp Depressive Disorder/ |
| 18 | exp Antidepressive Agents/ |
| 19 | or/16-18 |
| 20 | intervention$.ti,ab. |
| 21 | therapy.ti,ab. |
| 22 | management.ti,ab. |
| 23 | program$.ti,ab. |
| 24 | exp Treatment Outcome/ |
| 25 | outcome$.ti,ab. |
| 26 | random$.ti,ab. |
| 27 | or/20-26 |
| 28 | 15 and 19 and 27 |
| 29 | limit 28 to (english language and yr="1990-2010") |

where: exp=explode; ti= title; ab=abstract; adj=adjacent; mp=title, abstract, subject heading.

*Paper received March 2011, accepted June 2011*