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Improving outcomes for patients with depression by enhancing antidepressant therapy with non-pharmacological interventions: A systematic review of reviews

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SUMMARY

Objective: To analyse literature reviews reporting outcomes of non-pharmacological interventions directed at improving the treatment of depression.

Methods: A review of English articles was performed in June 2009 using the following databases: PubMed, EMBASE, International Pharmaceutical Abstracts, Web of Science, PsycINFO and the Cochrane Library. Only review articles comparing traditional pharmacotherapy and interventions combining pharmacological and non-pharmacological treatments were included. Extraction of articles and quality assessment of included reviews was performed independently by two authors using the AMSTAR score.

Results: The articles in the final data set included research on psychotherapeutic, multifaceted and single-component interventions. Single-component interventions have failed to demonstrate improved outcome for patients with depression. Collaborative care and additional psychotherapy have been shown to provide more benefits for patients than pharmacotherapy alone. Both approaches have a small effect on short-term treatment, and psychotherapy is the most effective for long-term prognosis in terms of preventing relapse. **Conclusion:** Conclusions regarding the effects of adherence-improving and multifaceted interventions are fairly certain. However, the findings about the impact of combined psychotherapy and pharmacotherapy on the outcomes of depression remain tentative due to the methodological limitations of available reviews.

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Introduction

Depression is one of the most common and debilitating mental disorders, with a very high burden of disease. According to the World Health Organization, rates for depression will continue to rise over the next 20 years.¹ Antidepressant medication is the first-line treatment for moderate and severe depression.² However, 30–40% of patients do not respond sufficiently to an adequately performed first-line drug treatment.³

Furthermore, patients who do not respond to the first pharmacological treatment have a lower probability of responding to a second or third treatment. A number of pharmacological strategies, such as changing the dosage, augmentation or switching to a different drug, have been suggested but have shown limited success.⁴ These clinical observations have initiated a change in focus towards a more holistic and personalized approach to treatment strategy. Indeed, the treatment that appears to be suitable for an average study

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sample may not be the best for a particular patient in a specific clinical situation.³ Thus, the key question is how to optimize daily administration of the currently available pharmacological treatments for a particular patient in order to obtain the best therapeutic outcome. Most care for chronic illnesses occurs outside of physicians' offices and hospitals.⁵ Therefore, the identification of investigations that would provide improved outcomes for patients with depression in conjunction with traditional pharmacotherapy is of particular importance. Several approaches have been reported to be effective.

Non-adherence is one of the major barriers to successful treatment. Indeed, non-adherence in mood disorders has been estimated to range from 10% to 60%.⁶ As such, interventions directed towards enhancing medication adherence are believed to yield benefits for patients with depression. Furthermore, depression is associated with remarkably high rates of functional impairment. Independent of the specific treatment, components of psychiatric management and general 'psychotherapeutic support' should always be initiated and continued throughout treatment.² The National Institute for Health and Clinical Excellence (NICE) recommends that patients with severe, treatment-resistant or recurrent depression should receive a combination of antidepressant medication and individual cognitive-behavioural therapy (CBT).⁷ Given the fact that more than 80% of patients with depression are managed and treated in primary care,⁸ interventions targeted at health care professionals have also been proposed to improve the management of depression.⁹ Thus, the aim of this study was to analyse literature reviews reporting the outcome of non-pharmacological interventions directed towards improving the treatment of depression in order to describe different approaches to combine with pharmacotherapy, and their effect on the outcomes of depression such as reaching remission and preventing relapse.

Methods

The number of non-pharmacological interventions that aim to improve outcomes for patients with depression has increased with time. As systematic reviews become more abundant, there is potential for greater use of such over-arching research as a way of arranging findings from several reviews.¹⁰ This umbrella review focuses on a broad problem regarding current non-pharmacological research within the treatment of depression.

Data sources

The literature search was performed in June 2009 using the following databases: PubMed; EMBASE; International Pharmaceutical Abstracts; Web of Science; PsycINFO; and the Cochrane Library. The following MESH terms and keywords were used: 'depressive disorder'; 'antidepressive agents'; 'patient compliance'; 'medication adherence'; 'psychotherapy'; 'patient education'; 'disease management'; 'collaborative care'; 'monitoring'; and 'treatment outcome'. A time span from 2000 to 2009 was selected. The reference lists of relevant reviews were hand-searched to identify other studies of interest.

Study selection

A reviewer identified and screened the studies, and these were independently screened by a second reviewer. Both reviewers assessed the full text of all reviews in light of eligibility criteria. Disagreements were discussed and consensus was reached in all cases.

Types of studies

Only review articles written in the English language and involving human subjects were included in the search. A systematic review can be defined as 'a review of clearly formulated questions that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review'.¹¹ A review was eligible for inclusion if it described the search strategy or explicitly stated the studies included.

Types of participant

Reviews were excluded if they focused on conditions other than major depressive disorder. Reviews describing psychiatric diseases such as bipolar disorder, schizophrenia, epilepsy and Alzheimer's disease were also excluded.

Types of intervention

Studies involving the use of antidepressants as a secondary therapy, such as in cardiovascular disease, cancer or pain management, were excluded. In addition, studies involving the use of electroconvulsive therapy or augmentation, and articles focusing on side effects or screening for depression were excluded. Reviews describing the replacement of pharmacotherapy with another technology, such as light therapy, acupuncture and sleep deprivation, were also excluded. Further screening was performed in order to identify reviews that reported the use of an intervention together with pharmacotherapy to improve outcomes in depression. Finally, for an article to be included in this review, it had to compare pharmacotherapy with an intervention that combined pharmaceutical and non-pharmaceutical approaches with the purpose of achieving better outcomes for patients with depression. Possible interventions used in conjunction with antidepressants were assumed to be interventions that enhance compliance/adherence to medication, psychotherapy, education or disease management programmes (DMPs).

The methodological quality of the systematic reviews included in the final analysis was graded independently by two reviewers using the AMSTAR score, a measurement tool used for the assessment of systematic reviews that shows good reliability and validity.¹²

Results

Literature search

The initial search found 1092 relevant articles. After reviewing the abstracts, 38 full text articles were examined in more detail for eligibility; the remaining papers clearly did not meet the criteria. Of these 38 articles, 19 were included in the final data analysis. The search and selection process are illustrated

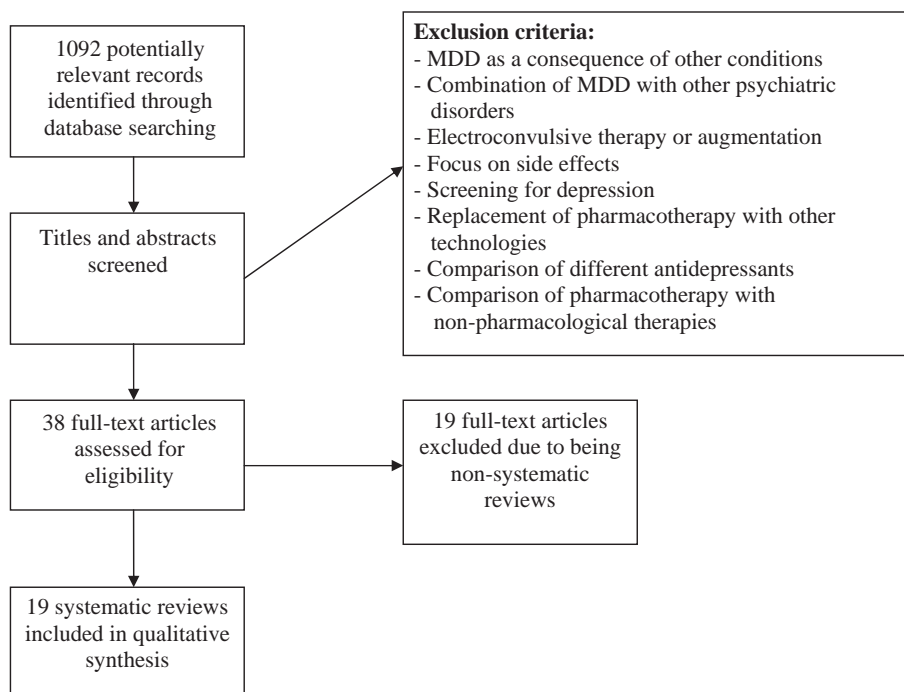


Fig. 1 – Flow diagram of the search and selection processes for reviews included in the study. MDD, major depressive disorder.

in Fig. 1, and the list of excluded studies is presented in Box 1. The articles in the final data set included research on psychotherapeutic, multifaceted organizational and single-component interventions. Of the 19 articles included, 13 were systematic reviews and six were meta-analyses.

Quality of the systematic reviews

Of the 13 systematic reviews, three were of low quality (AMSTAR score 0–4), seven were of moderate quality (AMSTAR score 5–8) and nine were of high quality (AMSTAR score 9–11) (Table 1). Five of the six meta-analyses were of high quality.

Adherence-improving interventions

Two systematic reviews and one meta-analysis described interventions affecting adherence to antidepressants. The mean AMSTAR score of these studies was 8.8, indicating a high level of quality.

Multifaceted interventions

Seven systematic reviews and three meta-analyses reported the influence of multifaceted interventions on the outcomes of depression. The mean AMSTAR score of these studies was 8.1, indicating a fairly high level of credibility of performed analyses.

Combined pharmacotherapy and psychotherapy

Five systematic reviews (mean AMSTAR score 4.8) and two meta-analyses (mean AMSTAR score 9.0) reported the influence of combined psychotherapy and pharmacotherapy interventions. The low level of quality of the systematic

reviews implies that the conclusions from these reviews are fairly uncertain. Therefore, further analysis of the influence of combined psychotherapy and pharmacotherapy on the outcomes of depression in this study will be based solely on the results of the meta-analyses.

Synthesis of evidence

Single-component interventions

Three articles (Table 2) were identified that reviewed single-component interventions aimed at improvement in the outcomes of depression. The number of included publications varied from nine to 32 studies (Table 1), with a total number of 58 individual publications. Fifty-two publications were only cited once, and six studies^{13–18} were included in two of the reviews. Two reviews investigated the influence of education on the outcomes of depression, and showed that interventions that concentrate exclusively on patient education do not improve outcomes. Bower et al.¹⁹ performed a meta-analysis to compare the effectiveness of counselling with usual general practitioner (GP) care. The results suggested that short-term counselling is significantly more effective than usual GP care [standardized mean difference (SMD) –0.28, 95% confidence interval (CI) –0.43 to –0.13; six trials], whereas long-term counselling does not provide an additional advantage over usual GP care (SMD 0.07, 95% CI –0.12 to 0.12; four trials).

Multifaceted interventions

Disease management and collaborative care are broad terms that describe the varied treatment packages proposed for improving the outcomes of depression in primary care. Ten

Box 1 Excluded non-systematic reviews listed alphabetically.

Anderson B. Collaborative care and motivational interviewing: improving depression outcomes through patient empowerment interventions. *Am J Manag Care* 2007; 13:S103–6.

Arnow BA, Constantino MJ. Effectiveness of psychotherapy and combination treatment for chronic depression. *J Clin Psychol* 2003; 59:893–905.

Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders. *World J Biol Psychiatry* 2002; 3:5–43.

Byrne N, Regan C, Livingston G. Adherence to treatment in mood disorders. *Curr Opin Psychiatry* 2006; 19:44–9.

Fava GA, Ruini C, Sonino N. Treatment of recurrent depression. *CNS Drugs* 2003; 17:1109–17.

Fava GA, Ruini C. What is the optimal treatment of mood and anxiety disorders? *Clin Psychol Sci Prac* 2005; 12:92–6.

Jackson B, Lurie S. Adolescent depression: challenges and opportunities. *Adv Pediatr* 2006; 53:111–63.

Katon WJ, Seelig M. Population-based care of depression: team care approaches to improving outcomes. *J Occup Environ Med* 2008; 50:459–67.

Keitner GI, Ryan CE, Solomon DA. Realistic expectations and a disease management model for depressed patients with persistent symptoms. *J Clin Psychiatry* 2006; 67:1412–21.

Kocsis JH. New strategies for treating chronic depression. *J Clin Psychiatry* 2000; 61:42–5.

Kupfer DJ. The interaction of drug- and psychotherapy in the long-term treatment of depression. *J Affect Disord* 2001; 62:131–7.

Miller MD. Using interpersonal therapy (ITP) with older adults today and tomorrow. *Curr Psychiatry Rep* 2008; 10:16–22.

Otto MW, Smits JAJ, Reese HE. Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults. *Clin Psychol Sci Prac* 2005; 12:72–86.

Petersen TJ. Enhancing the efficacy of antidepressants with psychotherapy. *J Psychopharmacol* 2006; 20:19–28.

Richmond TK, Rosen DS. The treatment of adolescent depression in the era of the black box warning. *Curr Opin Pediatr* 2005; 17:466–72.

Segal Z, Vincent P, Levitt A. Efficacy of combined, sequential and crossover psychotherapy and pharmacotherapy in improving outcomes in depression. *J Psychiatry Neurosci* 2002; 27:281–90.

Timonen M, Liukkonen T. Management of depression in adults. *BMJ* 2008; 336:435–9.

Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcome in patients with depression. *CNS Spectr* 2007; 12:1–27.

Varley CK. Treating depression in children and adolescents. *CNS Drugs* 2006; 20:1–13.

reviews (Table 2) describing the effects of primary care interventions were found. They included between five and 48 original publications, with a total number of 102 individual articles. Fifty-four publications were only cited once, and five publications^{20–24} were included most often (eight times) in the reviews.

Neumeier-Gromen *et al.*²⁵ performed a meta-analysis of homogeneous high quality randomized controlled trials investigating the effectiveness of DMPs for depression compared with usual primary care. It showed that DMPs had a significant effect on the severity of depression, with a relative risk of 0.75 (95% CI 0.70–0.81). The longest follow-up points with available data were used for each study, and included intervention durations from 4 to 12 months (acute to continuation phase). Approximately three-quarters of all participants were diagnosed with major depression. Other diagnoses included dysthymia, minor depression and subclinical disease levels. Studies where data were only available after 4 months of interventions included patients with minor and major depression in approximately equal proportions. DMP studies included five core characteristics: (1) different methods of patient education [book or videotape, homework, nurse, social worker, primary care physicians (PCP), study psychiatrists or psychologist]; (2) provider education; (3) different types of monitoring/care management (study psychiatrist, nurse/social worker/psychologist or independent psychiatrist); (4) collaborative care; and (5) different models of treatment focus (medication, psychotherapy, PCP, study psychiatrist or psychologist/psychiatrist). It was not possible to determine which single DMP elements were most effective.²⁵

The meta-analysis by Bower *et al.*²⁶ demonstrated a positive effect of collaborative care on the outcomes of depression with an SMD of 0.24 (95% CI 0.17–0.32). Eight variables were examined by univariate analysis to find associations between intervention content variables and depressive symptoms: study setting (outside the USA or within the USA), patient sample (patients with depression or patients willing to take antidepressants), recruitment method (referral or systematic identification), PCP training (no training or training provided), case manager background (non-mental or mental health professional), content of case management (medication management alone or combined with psychotherapeutic processes), supervision of case manager (none, variable or regular, and planned), and case management sessions (number of sessions as a continuous variable). Two intervention content variables were found to predict an improvement in depressive symptoms: case managers with professional expertise in mental health ($P = 0.004$), and the provision of regular supervision for case managers ($P = 0.033$). Furthermore, antidepressant use predicted depressive symptom outcomes ($P = 0.028$).

According to a meta-analysis by Gilbody *et al.*,²⁷ collaborative care had a positive effect on the outcomes of depression at 6 months compared with standard care (SMD 0.25, 95% CI 0.18–0.32). Data from 11 studies were used to assess the effect of collaborative care on long-term outcomes compared with standard care. The SMDs were 0.31 (95% CI 0.01–0.53), 0.25 (95% CI 0.03–0.46), 0.15 (95% CI -0.03 to 0.34) and 0.15 (95% CI 0.001–0.30) at 12 months, 18 months, 24 months and 5 years, respectively. There was substantial heterogeneity between studies used for assessment outcomes at 24 months. The use of

Table 1 – Quality of the included reviews on non-pharmacological interventions for improving the outcomes of depression.

Reviews by type	Adherence-improving interventions		Multifaceted interventions		Combined psychotherapy and pharmacotherapy	
	AMSTAR score	No. of studies included	AMSTAR score	No. of studies included	AMSTAR score	No. of studies included
<i>Systematic reviews</i>						
Adli et al., 2006 ³			4	14		
Fava et al., 2005 ⁵¹					3	29
Freudenstein et al., 2001 ⁵²			9	5		
Gilbody et al., 2003 ²⁹			6	36		
Gunn et al., 2006 ³⁰			9	11		
Hegerl et al., 2004 ⁵³					5	10
Hollon et al., 2005 ⁵⁴					3	64
Kates et al., 2007 ⁴¹			5	18		
Michalak et al., 2002 ⁵⁵					7	8
Pampallona et al., 2002 ³⁶	9	32				
Stein et al., 2006 ⁵⁶					6	37
Vergouwen et al., 2003 ⁵⁷	8	9	8	11		
Williams et al., 2007 ²⁸			9	28		
Mean	8.5	20.5	7.1	17.6	4.8	29.6
<i>Meta-analyses</i>						
Bower et al., 2003 ¹⁹	9	12				
Bower et al., 2006 ²⁶			9	48		
Friedman et al., 2004 ³²					8	20
Gilbody et al., 2006 ²⁷			9	37		
Neumeyer-Gromen et al., 2004 ²⁵			9	13		
Pampallona et al., 2004 ³³					10	16
Mean	9.0	12.0	9.0	32.7	9.0	18.0
Overall mean	8.8	16.3	8.1	25.1	6.9	23.8

regular and planned supervision of the case manager was related to a more positive clinical outcome ($P = 0.07$). The mental health background of case managers was also significantly related to the effect size ($P = 0.02$). Neither the addition of a specific form of psychotherapy to medication management ($P = 0.20$) nor the duration of case management and number of case sessions ($P = 0.19$) were related to the effect size.

Some studies have reported that management delivered exclusively or predominantly by telephone shows improved outcomes for depression.^{28,29} All studies emphasized that the perception of depression has shifted from viewing this disease as an acute condition to viewing this disease as a chronic disorder.^{28,30} Therefore, the organization of care should be as for other chronic illnesses.

Integrated psychotherapy

Seven articles (Table 2) comparing pharmacotherapy alone with a combination of psychotherapy and pharmacotherapy were identified. The number of original articles included in these reviews varied between eight and 64 (Table 1), with a total of 158 individual publications. A study by Keller et al.³¹ was included most often in the reviews (five times). The psychotherapeutic techniques used in these studies were cognitive therapy, CBT, interpersonal therapy (IPT), cognitive-behavioural-analysis system of psychotherapy and mindfulness-based cognitive therapy. Patients with chronic or recurrent depression, adolescents and geriatric patients, and patients with moderate and severe depression benefit most from the introduction of combined treatment.

Friedman et al.³² performed a meta-analysis of 20 studies comparing combined treatment and pharmacotherapy that were delivered in acute and maintenance phases. The results demonstrated that combined therapy has a small benefit in reaching remission compared with medication alone during acute phase treatment (effect size Cohen's $d = 0.30$). However, combined psychotherapy and pharmacotherapy showed a moderate effect in reduced relapse rates compared with medication alone ($d = 0.68$). The largest effect of combined treatment was found in preventing relapse, compared with medication alone, in studies of naturalistic follow-ups or among patients discontinuing medication. The effect of CBT seems to continue over long-term follow-up regardless of whether CBT is delivered in the acute phase or the maintenance phase.³² A meta-analysis performed by Pampallona et al., based on 16 trials, showed that patients receiving combined treatment improved significantly compared with those receiving drug treatment alone [odds ratio (OR) 1.86, 95% CI 1.39–2.52]. Studies lasting for longer than 12 weeks showed a significant advantage of combined treatment over drug treatment alone (OR 2.21, 95% CI 1.22–4.03), with a significant reduction in dropouts compared with non-responders (OR 0.59, 95% CI 0.39–0.88).³³

Some studies have explored the influence of the design of psychotherapy and pharmacotherapy integration, such as concurrent (or simultaneous) and sequential (or crossover) treatment.⁴ The simultaneous administration of pharmacotherapy and psychotherapy in the acute phase only results in a modest improvement; however, a sequential strategy based on the use of pharmacotherapy in the acute phase and

Table 2 – Description of the included studies.

Review (AMSTAR score)	Description	Main results
<i>Adherence-improving interventions</i> Pampallona <i>et al.</i> , 2002 ³⁶ (9)	Thirty-two studies published between 1973 and 1999: epidemiological descriptive studies (14), non-random comparisons of control and intervention groups (3), randomized interventions (14), meta-analysis (1). Studies were conducted in the UK (10), Canada (3), Europe (3) and the USA (16). Patients with major depression (5), major and minor depression (5), mixed diagnosis with depression (10), unspecified depressive disorder (11)	Patient education and medication clinics were the interventions most commonly tested. It was not possible to extract meaningful indications on factors associated with non-adherence
Vergouwen <i>et al.</i> , 2003 ⁵⁷ (8)	Interventions directed at education. Nine studies, all RCTs. Studies were conducted in the UK (6), the USA (1) and Italy (1). Patients with major depression (2), unspecified depressive disorder (7)	Failed to demonstrate a clear benefit on outcomes of depression
Bower <i>et al.</i> , 2003 ¹⁹ (9)	Counselling vs usual care for short and long-term outcomes. Twelve studies: RCTs and controlled clinical trials of high quality. All studies were conducted in the UK. Patients with major depression (4), mixed diagnosis with depression (4), unspecified depressive disorder (4)	Significantly greater clinical effectiveness of counselling compared with usual general practitioner care in the short-term (SMD -0.28; six trials) but not the long-term (SMD -0.07; four trials)
<i>Multifaceted interventions</i> Adli <i>et al.</i> , 2006 ³ (4)	Effects of algorithm-guided treatment of depression. Fourteen studies: open controlled studies (3), RCTs (11). Studies were conducted in the USA (10), Canada (1), the UK (1) and Germany (2). Patients with major depression (8), mixed depression (4), unspecified depression (2)	Increase the efficacy of applied treatments
Freudenstein <i>et al.</i> , 2001 ⁵² (9)	Treatment for depression of patients over 60 years of age in primary care. Five studies: all RCTs with quality criteria by the Cochrane Effective Practice and Organization of Care Group. Studies were conducted in the UK (2), Sweden (1), Norway (1) and France (1). Patients with major depression (3), unspecified depression (2)	There is little evidence of effectiveness for a variety of treatment approaches in older people in primary care
Gilbody <i>et al.</i> , 2003 ²⁹ (6)	Effectiveness of organizational and educational interventions to improve the management of depression in primary care. Thirty-six studies: RCTs (29), controlled before-and-after studies (5), interrupted time-series analyses (2). Studies were conducted in the USA (22), the UK (9), Sweden (1), Finland (1), Canada (1) and the Netherlands (2). Patients with major depression (5), mixed diagnosis with depression (8), unspecified depression (23)	Strategies effective in improving patient outcome were generally those with complex interventions that incorporated clinician education, an enhanced nurse role, and a greater degree of integration between primary and secondary care
Gunn <i>et al.</i> , 2006 ³⁰ (9)	Chronic illness management approaches for depression in primary care. Eleven studies: all RCTs with quality in accordance with CONSORT criteria. Studies were conducted in the USA (10) and the UK (1). Patients with major depression (6), unspecified depression (5)	System-level interventions led to a modest increase in recovery
Kates and Mach, 2007 ⁴¹ (5)	Chronic disease management models for depression in primary care. Eighteen studies: all RCTs. All studies were conducted in the USA. Patients with major depression (5), mixed diagnosis with depression (5), unspecified depression (8)	Changing systems of care delivery to support the more effective management of depression in primary care would lead to benefits
Vergouwen <i>et al.</i> , 2003 ⁵⁷ (8)	Eleven studies: all RCTs. Studies were conducted in the USA (9) and the UK (2). Patients with major depression (1), major and minor depression (2), mixed diagnosis with depression (4), unspecified depression (3)	Collaborative care interventions are associated with clinical benefit
Williams <i>et al.</i> , 2007 ²⁸ (9)	Twenty-eight studies: all RCTs. Studies were conducted in the USA (22), the UK (3), Chile (1) and the Netherlands (1). Patients with major depression (7), minor and major depression (2), mixed diagnosis with depression (6), unspecified depression (11)	The most commonly used intervention features were: patient education and self-management, monitoring of depressive symptoms and treatment adherence, decision support for medication management, a patient registry and mental health supervision of care managers

Bower et al., 2006 ²⁶ (9)	Examination of the relationship between the content of collaborative care and outcomes. Forty-eight studies: all RCTs. Studies were conducted in the USA (40), the UK (4), the Netherlands (2), Chile (1) and Sweden (1). Patients with major depression (23), major and minor depression (3), mixed diagnosis with depression (5), unspecified depression (15)	Positive effect of collaborative care on depression outcomes with SMD of 0.24 (95% CI 0.17–0.32)
Gilbody et al., 2006 ²⁷ (9)	Explore the clinical effectiveness of collaborative care in the short and long-term. Thirty-seven studies: all RCTs. Studies were conducted in the USA (28), the UK (4), the Netherlands (1), Sweden (1) and Chile (1). Patients with major depression (9), mixed diagnosis with depression (8), unspecified depression (18)	Collaborative care has a positive effect on standardized depression outcomes at 6, 12, 18 and 24 months, and 5 years with SMDs of 0.25, 0.31, 0.25, 0.15 and 0.15, respectively
Neumeyer-Gromen et al., 2004 ²⁵ (9)	Effectiveness of disease management programmes for depression. Ten studies: all RCTs of A/B (Cochrane Collaboration guidelines) quality. All studies were conducted in the USA. Patients with major depression (3), major and minor depression (2), mixed diagnosis with depression (1), unspecified depression (4)	Disease management programmes have a significant effect on depression severity with a relative risk of 0.75 (95% CI 0.70–0.81) for interventions with a duration of 4–12 months
<i>Combined psychotherapy and pharmacotherapy</i>		
Fava et al., 2005 ⁵¹ (3)	Sequential use of pharmacotherapy and psychotherapy, CBT and MBCT. Twenty-nine studies: RCTs (24), epidemiological (5). Studies were conducted in the USA (12), the UK (7), Italy (8) and the Netherlands (2). Patients with major depression (15), major and minor depression (1), mixed diagnosis with depression (8), unspecified depression (5)	Further investigations are needed
Hegerl et al., 2004 ⁵³ (5)	Analysis of usefulness of combined pharmacotherapy and psychotherapy vs pharmacotherapy or psychotherapy alone. Ten studies: RCTs (7), meta-analyses (3). Studies were conducted in the USA (5), the UK (2) and Germany (2). Patients with major depression (4), unspecified depression (6)	There is no significant superiority of a combined therapy over medication alone. Older patients and patients with severe or chronic depression might benefit from combined therapy.
Hollon et al., 2005 ⁵⁴ (3)	Efficacy of medications and psychotherapy alone and in combination for adult and geriatric depression. Sixty-four studies: meta-analyses (2), RCTs (46), epidemiological descriptive studies (12), non-random comparisons of control and intervention groups (5). Studies were conducted in the USA (45), the UK (7), Italy (3), the Netherlands (2), Switzerland (1), Canada (2). Patients with major depression (29), mixed diagnosis with depression (9), unspecified depression (26)	Treatment with a combination of medication and IPT or CBT retains the specific benefits of each and may enhance the probability of a response over either monotherapy, especially in chronic depression
Michalak and Lam, 2002 ⁵⁵ (7)	Treatment of chronic depression. Eight studies: RCTs (7), meta-analysis (1). Studies were conducted in the USA (4), Canada (2) and the UK (1). Patients with dysthymia (5), chronic major depression (2), mixed diagnosis with depression (1)	A combination of pharmacotherapy and psychotherapy is an effective, safe and possibly superior form of treatment for chronic depression
Friedman et al., 2004 ³² (8)	To clarify the efficacy of combined treatment for depression. Twenty studies: all RCTs. Studies were conducted in the USA (14), the UK (4) and the Netherlands (1). Patients with major depression (10), unspecified depression (9)	Small improvement of combined treatment in efficacy for remission ($d = 0.30$), and particularly efficacious in preventing relapse ($d = 0.68$)
Pampallona et al., 2004 ³³ (10)	To study the relationship between efficacy of antidepressant drugs plus psychological treatment vs drug treatment alone. Sixteen studies: all RCTs. Studies were conducted in the USA (9), Canada (2), the UK (3), the Netherlands (1) and Switzerland (1). Patients with major depression (10), dysthymic disorder (3), unipolar depression (2), mixed diagnosis with depression (1)	Patients receiving combined treatment improved significantly compared with those receiving drug treatment alone (OR 1.86, 95% CI 1.38–2.52); for studies longer than 12 weeks: OR 2.21 (95% CI 1.22–4.03)
Stein et al., 2006 ⁵⁶ (6)	Psychological, educational and/or supportive intervention strategies for adolescent depression. Thirty-seven studies: RCTs (20), simple before-and-after studies (9), controlled before-and-after studies (9). Studies were conducted in the USA, the UK, Australia and the Netherlands. Patients with major depression, mixed depression or unspecified depression (majority)	Psychosocial interventions can be effective
RCT, randomized controlled trial; SMD, standardized mean difference; CI, confidence interval; OR, odds ratio; CBT, cognitive-behavioural therapy; MBCT, mindfulness-based cognitive therapy; IPT, interpersonal therapy.		

cognitive therapy for residual symptoms has shown evidence of being beneficial in preventing relapse and recurrence. Importantly, this sequential model introduces a conceptual shift in therapeutic practice, and might represent a way to enhance long-term recovery from depression.

Discussion

This study reviewed reviews of non-pharmacological interventions that can be used to supplement traditional pharmacotherapy in order to improve remission rates and prevent relapse in patients with depression. The interventions that were identified ranged from simple methods, such as telephone counselling or patient education, to complex multimodal approaches involving large health care organizations and requiring major organizational changes.

The following limitations of this study have to be mentioned. First, the search was limited to English language publications. Second, the quality of the included reviews varied, with the highest quality reviews describing multifaceted interventions and adherence-improving interventions (mean AMSTAR scores of 8.1 and 8.8, respectively). Furthermore, the level of overlapping studies included in different reviews was quite high for multifaceted interventions, reflecting consistency in results as well as saturation of performed searches. Reviews describing adherence-improving interventions were of high quality, but with a very modest level of overlapping of included studies. This fact could indicate a very broad and comprehensive searching strategy among the reviews. Finally, reviews investigating the influence of psychotherapy were of relatively low quality, with a moderate level of overlapping of included studies. Thirdly, the choice of interventions improving outcomes for depression included in this review was inspired by recommendations provided by NICE,⁷ however, restriction to multifaceted interventions, combined pharmacotherapy and psychotherapy, and interventions improving adherence was, to a certain extent, arbitrary. Therefore, this represents another drawback of the study.

Reviews published before 2000 were not included in this study. Systematic reviews are an important tool for different medical stakeholders. However, as shown in this study, the quality of reporting is inconsistent. This finding is in line with previous publications.³⁴ One way to improve such shortcomings of published reviews is to provide explicit reporting guidelines, as was the case for improved reporting of randomized controlled trials after the introduction of the CONSORT Statement. Similarly, the QUORUM Statement that was proposed in 1999³⁵ aimed to improve the quality of reporting for meta-analyses. The authors considered that systematic reviews published since 1999 were likely to be of better quality, so a time span after 2000 was selected.

One way to improve outcome and decrease the risk of relapse in mood disorders is to enhance adherence. Indeed, non-adherence is a major problem in the treatment of depression, and it is estimated that around 40% of patients do not take their prescribed medicine properly.^{6,36} The present findings show that simple educational strategies have a minimal effect on depression symptoms, which is in line with

previous studies.^{6,29} Although some studies have shown that antidepressant use did predict the outcome of depressive symptoms,²⁶ other studies have reported that the relationship between adherence and outcome is often not clear and consistent.⁶ Adherence behaviour represents a challenge for health care professionals, not only due to the complexity of reasons for non-adherence but also due to problems related to methodical assessment. As well as a lack of consensus about how adherence should be measured, the interpretation of adherence results is also very complicated.⁶ Therefore, a conclusion about the effectiveness of interventions influencing adherence should be based on studies that have followed patients to full remission and where adherence was specifically measured. Even then, the question would still be whether the remission was actually due to treatment or spontaneous. In spite of the fact that educational interventions have been shown to be ineffective as single approaches, they are successful when accompanied by complex organizational interventions, such as nurse management, collaborative care, a depression management programme or an intensive quality improvement initiative.²⁹

Collaborative care, as an approach of co-ordinated interventions that incorporate the efforts of several different providers in managed care, has been shown to be effective for improving outcomes in patients with depression.^{27,28,37} The productive interaction between patients and primary care providers (PCPs) is also seen as one of the important characteristics of successful collaborative care. The goal of such interactions is a situation in which patients and their PCPs work together to find the most effective medication and, perhaps, lifestyle changes to manage illness.⁵ Thus, the development of training initiatives for both PCPs and patients is needed in the future.

Another feature of the collaborative care model is shifting the view of depression from being an acute condition to a chronic disorder, much like asthma.⁵ As a consequence, the chronic illness model developed by Wagner *et al.*³⁸ and used for other chronic conditions may also be applied to mood disorders. Chronic care is characterized by the interaction of a prepared, proactive practice team and an informed, active patient who is able to self-manage the chronic illness rather than playing the passive role that is more typical of the traditional medical model.³⁸ Furthermore, self-management support, which involves both collaborative care and self-management education, is believed to be the core of the chronic care model.³⁹ Some investigations have suggested that focusing on a patient's well-being, quality of life, interpersonal functioning and coping skills as primary outcomes is a more realistic goal than concentrating on depressive symptoms.⁴⁰ The challenge is that failures in many personal characteristics, such as well-being or social functioning, are common components of depressive symptoms. Therefore, the separation of personal difficulties and depressive symptoms is not straightforward.

Although multifaceted interventions have shown improved outcomes for patients with depression, it is still not clear which components of these complex interventions are most likely to have beneficial outcomes.^{3,29,41} Indeed, different authors include various elements as crucial in a successful intervention. Adli *et al.*³ reported that two active elements are required

for a successful treatment algorithm: the specific treatments used at each step; and a diligent, highly structured approach to monitoring treatment results and adjusting treatment. Gilbody *et al.*²⁷ reported three elements of collaborative care: a case manager, a PCP and access to a specialist that can provide effective treatment. Katon and Seelig⁵ demonstrated that effective collaborative care should include two key components: the use of depression care managers to increase the frequency of patient contacts, and consultation by a psychiatrist. Williams *et al.*²⁸ reported that care management, a key component of intervention, should include up to five functions (communication and co-ordination of care, education and support, monitoring of symptoms and adherence, self-management support, psychological treatments) and five processes (duration, number of contacts, type of contacts, care manager discipline, mental health supervision). Another common component within successful interventions is involvement in the active follow-up of patients.²⁹ Taken together, it is difficult to operate with primary care interventions that recommend several separately developed DMPs, each with their own training and resource requirements.⁶

Almost all multifaceted interventions lead to clinically important improvements in short-term outcomes of depression. The effect sizes reported by different researchers^{26,27} showed similar results with SMD of 0.24–0.25. The same small effect was reported to continue for up to 5 years (SMD 0.15).²⁷ DMPs may reduce the severity of depression by 25%, with potential benefit ranging from a 19% to a 30% reduction in risk according to the meta-analysis performed by Neumeier-Gromen *et al.*²⁵ Collectively, collaborative care involves the co-ordination of efforts between different levels of providers in managed care, and captures a range of patient support interventions of varying intensity, from simple telephone support to encourage medication adherence to more complex programmes that involve intensive follow-up and incorporate a form of structured psychosocial intervention.³⁷

Any successful collaborative care intervention contains an element of psychological support provided in different ways. A small effect size was found for psychotherapy combined with pharmacology for short-term interventions ($d = 0.30$). However, the effect size was found to be moderate for long-term interventions ($d = 0.68$).³² Pampallona *et al.*³³ showed that patients receiving combined treatment were 1.86–2.21 times more likely to experience remission compared with those receiving pharmacotherapy alone. Thus, although the addition of psychotherapy to the acute phase of depression shows a small effect size, combined therapy provides a substantial benefit for long-term prognosis in terms of preventing relapse, especially for patients with chronic or recurrent disorders, and adolescent and geriatric patients.

Many studies have reported that psychotherapy might have an adherence-enhancing role.^{32,33,42} The addition of psychotherapy reduces non-response rates and helps to keep patients in treatment.³³ In addition, psychotherapy may make some patients more amenable to antidepressant therapy.⁴² Psychotherapy yields effects that are not provided by antidepressants, such as an improvement in the quality of interpersonal relationships and coping skills. Some research indicates that the inclusion of two separate approaches for the treatment of

depression (e.g. psychotherapy and medication) may trigger very different mechanisms and pathways of action.^{32,42}

Although combination treatment is the first recommendation for the treatment of moderate and severe depression, several barriers to the implementation of this strategy should be noted. It is often difficult to obtain access to mental health practitioners, particularly child and adolescent psychiatrists. Thus, decisions to treat are often left in the hands of primary care providers.⁴³ However, many practitioners are not familiar with the psychotherapies that have been tested for depression, such as CBT and IPT.^{43,44} On the other hand, some studies have also reported that the basic principles of IPT can be taught quickly to a variety of clinicians.⁴⁵

Another problem is that psychotherapy may not be available in certain geographic areas.⁴⁶ In such cases, computer support systems, self-reports, web-based e-mail or telephone-based assistance can be used for the delivery of mental health care. The internet is expected to bring radical changes in medical and health care.⁴⁷ Several studies have been performed to explore the effect of internet-based CBT programmes on depression and other mental illnesses.^{48–50} It has been reported that remote interventions have the potential to overcome some of the barriers to traditional psychological therapy services. Thus, future efforts should be directed towards the development of optimal depression packages for patients and providers, as well as towards training in the use of these programmes.

Due to the methodological limitations of the included reviews, caution should be taken regarding the effectiveness of different non-pharmacological interventions on outcomes of depression. Conclusions regarding adherence-improving and multifaceted interventions are based on good quality studies and, therefore, are fairly certain. However, only a few studies reporting the effects of combined psychotherapy and pharmacotherapy are of high quality; therefore, further research within this approach is needed, and the findings about the impact of combined therapy on the outcomes of depression should remain tentative at present.

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Competing interests

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