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Prevention of depression in adults with long-term physical conditions (Review)

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[Intervention Review]

Prevention of depression in adults with long-term physical conditions

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A B S T R A C T

Background

Major depression is one of the world's leading causes of disability in adults with long-term physical conditions compared to those without physical illness. This co-morbidity is associated with a negative prognosis in terms of increased morbidity and mortality rates, increased healthcare costs, decreased adherence to treatment regimens, and a substantial decline in quality of life. Therefore, preventing the onset of depressive episodes in adults with long-term physical conditions should be a global healthcare aim.

In this review, primary or tertiary (in cases of preventing recurrences in those with a history of depression) prevention are the focus. While primary prevention aims at preventing the onset of depression, tertiary prevention comprises both preventing recurrences and prohibiting relapses. Tertiary prevention aims to address a depressive episode that might still be present, is about to subside, or has recently resolved. We included tertiary prevention in the case where the focus was preventing the onset of depression in those with a history of depression (preventing recurrences) but excluded it if it specifically focused on maintaining an condition or implementing rehabilitation services (relapse prevention). Secondary prevention of depression seeks to prevent the progression of depressive symptoms by early detection and treatment and may therefore be considered a 'treatment,' rather than prevention. We therefore exclude the whole spectrum of secondary prevention.

Objectives

To assess the effectiveness, acceptability and tolerability of psychological or pharmacological interventions, in comparison to control conditions, in preventing depression in adults with long-term physical conditions; either before first ever onset of depressive symptoms (i.e. primary prevention) or before first onset of depressive symptoms in patients with a history of depression (i.e. tertiary prevention).

Search methods

We searched the Cochrane Common Mental Disorders Controlled Trials Register, CENTRAL, MEDLINE, Embase, PsycINFO and two trials registries, up to 6 February 2020.

Selection criteria

We included randomised controlled trials (RCTs) of preventive psychological or pharmacological interventions, specifically targeting incidence of depression in comparison to treatment as usual (TAU), waiting list, attention/psychological placebo, or placebo. Participants had to be age 18 years or older, with at least one long-term physical condition, and no diagnosis of major depression at baseline (primary prevention). In addition, we included studies comprising mixed samples of patients with and without a history of depression, which explored tertiary prevention of recurrent depression. We excluded other tertiary prevention studies. We also excluded secondary

preventive interventions. Primary outcomes included incidence of depression, tolerability, and acceptability. Secondary outcomes included severity of depression, cost-effectiveness and cost-utility.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.

Main results

We included 11 RCTs, with one trial on psychological interventions, and 10 trials on pharmacological interventions. Data analyses on the psychological intervention (problem-solving therapy compared to TAU) included 194 participants with age-related macular degeneration.

Data analyses on pharmacological interventions included 837 participants comparing citalopram (one trial), escitalopram (three trials), a mixed sample of fluoxetine/nortriptyline (one trial), melatonin (one trial), milnacipran (one trial), and sertraline (three trials), each to placebo. Included types of long-term physical conditions were acute coronary syndrome (one trial), breast cancer (one trial), head and neck cancer (two trials), stroke (five trials), and traumatic brain injury (one trial).

Psychological interventions

Very low-certainty evidence of one study suggests that problem solving therapy may be slightly more effective than TAU in preventing the incidence of depression, immediately post-intervention (odds ratio (OR) 0.43, 95% confidence interval (CI) 0.20 to 0.95; 194 participants). However, there may be little to no difference between groups at six months follow-up (OR 0.71, 95% CI 0.36 to 1.38; 190 participants; one study; very low-certainty evidence). No data were available regarding incidence of depression after six months. Regarding acceptability (drop-outs due to any cause), slightly fewer drop-outs occurred in the TAU group immediately post-intervention (OR 5.21, 95% CI 1.11 to 24.40; 206 participants; low-certainty evidence). After six months, however, the groups did not differ (OR 1.67, 95% CI 0.58 to 4.77; 206 participants; low-certainty evidence). This study did not measure tolerability.

Pharmacological interventions

Post-intervention, compared to placebo, antidepressants may be beneficial in preventing depression in adults with different types of long-term physical conditions, but the evidence is very uncertain (OR 0.31, 95% CI 0.20 to 0.49; 814 participants; nine studies; I^2 =0%; very low-certainty evidence). There may be little to no difference between groups both immediately and at six months follow-up (OR 0.44, 95% CI 0.08 to 2.46; 23 participants; one study; very low-certainty evidence) as well as at six to 12 months follow-up (OR 0.81, 95% CI 0.23 to 2.82; 233 participants; three studies; I^2 = 49%; very low-certainty evidence). There was very low-certainty evidence from five studies regarding the tolerability of the pharmacological intervention. A total of 669 adverse events were observed in 316 participants from the pharmacological intervention group, and 610 adverse events from 311 participants in the placebo group. There was very low-certainty evidence that drop-outs due to adverse events may be less frequent in the placebo group (OR 2.05, 95% CI 1.07 to 3.89; 561 participants; five studies; I^2 = 0%). There was also very low-certainty evidence that drop-outs due to any cause may not differ between groups either post-intervention (OR 1.13, 95% CI 0.73 to 1.73; 962 participants; nine studies; I^2 = 28%), or at six to 12 months (OR 1.13, 95% CI 0.69 to 1.86; 327 participants; three studies; I^2 = 0%).

Authors' conclusions

Based on evidence of very low certainty, our results may indicate the benefit of pharmacological interventions, during or directly after preventive treatment. Few trials examined short-term outcomes up to six months, nor the follow-up effects at six to 12 months, with studies suffering from great numbers of drop-outs and inconclusive results. Generalisation of results is limited as study populations and treatment regimes were very heterogeneous.

Based on the results of this review, we conclude that for adults with long-term physical conditions, there is only very uncertain evidence regarding the implementation of any primary preventive interventions (psychological/pharmacological) for depression.

PLAIN LANGUAGE SUMMARY

Drug or psychological interventions for preventing depression in people with long-term physical conditions

Why is this review important?

People with long-term illness or other physical health conditions have a higher risk than other people of developing depression. This can reduce their quality of life. Depression is characterised by symptoms such as low mood, feelings of hopelessness, loss of interest in things that once gave pleasure, and other symptoms, as well as sleep disturbances. People with long-term physical conditions who develop depression are more likely to worsen in their illnesses and are more likely to die. Therefore, preventing depression in people with long-term physical conditions should be an important goal in healthcare.

What questions does this review aim to answer?

We wanted to know whether standard interventions for treating depression (i.e. psychological treatments and antidepressant drugs) can also safely be used to prevent the onset of an depressive episode in those adults at high risk for depression due to their long-term physical condition, but who do not yet show depressive symptoms. We also wanted to know whether these interventions worked in preventing recurrent depression, in those patients with long-term physical conditions who had a history of depression.

How did we identify and evaluate the evidence?

First, we searched the medical literature for randomised controlled studies (clinical studies where people are randomly put into one of two or more treatment groups). This type of study provides the most robust evidence about the effects of a treatment. We then compared the results, and summarised the evidence from all the studies. Finally, we assessed how certain the evidence was. To do this, we considered factors such as the way studies were conducted, study sizes, and consistency of findings across studies. Based on our assessments, we categorised the evidence as being of very low, low, moderate or high certainty.

Who will be interested in this review?

Medical and mental health care providers (including physicians and psychologists) and pharmacists, as well as adults with long-term physical conditions, their relatives and care-givers.

Which studies were included in the review?

This review includes 11 trials comparing a psychological intervention (problem-solving therapy) to treatment as usual; or comparing pharmacological antidepressant interventions (citalopram, escitalopram, sertraline, fluoxetine/nortriptyline, milnacipran, or melatonin) to placebo. For the psychological intervention, we found only one trial, including 194 people with age-related macular degeneration (an eye disease). For pharmacological interventions, we included 10 trials comprising 1009 people. Due to some participants not completing the studies, we could only analyse data for 837 participants.

What does the evidence from the review tell us?

Our analyses show that people with long-term physical conditions may be less likely to develop depression during treatment with problem solving therapy, or with different types of antidepressants. However, these interventions appear to be beneficial only during treatment. Three to 12 months after treatment, there was no significant difference in onset of depression between the groups that had the interventions and those that did not. Therefore, preventive interventions might be effective in preventing depression onset only for the duration of the intervention. Our conclusions are based on evidence of very low certainty. In addition, there is not enough adequate information on the tolerability (unpleasant but generally medically less important adverse events due to the intervention, e.g. dry mouth) and acceptability (willingness to go through with the intervention even in the presence of adverse events) of these treatments. The interventions may be unsafe, irrespective of their potential to prevent depression.

How-up-to date is this review?

The evidence in this Cochrane Review is current to 6 February 2020.

SUMMARY OF FINDINGS

Summary of findings 1.   Psychological interventions compared to treatment as usual in the prevention of the incidence of depression in adults with long-term physical conditions

Psychological interventions compared to treatment as usual in the prevention of the incidence of depression in adults with long-term physical conditions

Patient or population: adults with long-term physical conditions (18 years or older)
Setting: hospital
Intervention: preventive psychological interventions
Comparison: treatment as usual

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with treatment as usual	Risk with preventive psychological interventions				
Incidence of depression - post-intervention: 0 months follow-up assessed with: diagnosis by DSM-IV	Study population		OR 0.43 (0.20 to 0.95)	194 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2][3][4]	
	23 per 100	12 per 100 (6 to 22)				
Incidence of depression - short term: < 6 months follow-up assessed with: diagnosis by DSM-IV	Study population		OR 0.71 (0.36 to 1.38)	190 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2][3][4]	
	27 per 100	21 per 100 (12 to 34)				
Incidence of depression - medium term: 6-12 months follow-up	no data available		-	(0 RCTs)	-	
Incidence of depression - long term: > 12 months follow-up	no data available		-	(0 RCTs)	-	
Tolerability - total number of adverse events	no data available		-	(0 RCTs)	-	
acceptability - drop-outs due to adverse events	no data available		-	(0 RCTs)	-	
acceptability - drop-outs due to any cause: post-intervention	Study population		OR 5.21 (1.11 to 24.40)	206 (1 RCT)	⊕⊕⊖⊖ LOW [2][4]	
	20 per 1.000	95 per 1.000 (22 to 330)				

| acceptability - drop-outs due to any cause: < 6 months | Study population | | OR 1.67 (0.58 to 4.77) | 206 (1 RCT) | ⊕⊕⊝⊝ LOW [2][4] |
| | 59 per 1.000 | 95 per 1.000 (35 to 232) | | | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio;

__GRADE Working Group grades of evidence__
__High certainty:__ We are very confident that the true effect lies close to that of the estimate of the effect
__Moderate certainty:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
__Low certainty:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
__Very low certainty:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The low and high risk values are the two extreme numbers of incidences in the control groups from studies included in the review.
[2] Downgraded once due to indirectness. Due to the nature of this review, we included all types of chronic physical illnesses. With only one study addressing psychological interventions, there is some uncertainty with the applicability of the effect to all types of diseases.
[3] Downgraded once due to imprecision. The evidence is based on only one study with 194 participants.
[4] Publication bias strongly suspected.

Summary of findings 2.   Pharmacological interventions compared to placebo in the prevention of the incidence of depression in adults with long-term physical conditions

__Pharmacological interventions compared to placebo in the prevention of the incidence of depression in adults with long-term physical conditions__

__Patient or population:__ adults with long-term physical conditions (18 years or older)
__Setting:__ hospitals (especially university medical center) and specialised rehabilitation clinics
__Intervention:__ preventive pharmacological interventions
__Comparison:__ placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with preventive pharmacological interventions				
Incidence of depression - post-intervention: 0 months follow-up assessed with: diagnosis by DSM-IV, ICD-10 or clinician, & cut-off (HADS-D, MDI, QIDS-RS, HAM-D-17)	Study population		OR 0.31 (0.20 to 0.49)	814 (9 RCTs)	⊕⊝⊝⊝ VERY LOW [1][2][4][5]	
	22 per 100	8 per 100 (5 to 12)				

			OR	N	Certainty
	Low				
	6 per 100 [3]	2 per 100 (1 to 3)			
	High				
	28 per 100 [3]	11 per 100 (7 to 16)			
Incidence of depression - short-term: < 6 months follow-up assessed with: diagnosis by clinician	Study population		OR 0.44 (0.08 to 2.46)	23 (1 RCT)	⊕⊝⊝⊝ VERY LOW [2 4 5 6]
	50 per 100	22 per 100 (4 to 100)			
Incidence of depression - medium-term: 6-12 months follow-up assessed with: diagnosis by DSM-IV	Study population		OR 0.81 (0.23 to 2.82)	233 (3 RCTs)	⊕⊝⊝⊝ VERY LOW [2 4 5 7 8]
	18 per 100	16 per 100 (5 to 39)			
	Low				
	0 per 100 [3]	0 per 100 (0 to 0)			
	High				
	30 per 100 [3]	26 per 100 (9 to 55)			
Incidence of depression - long-term: >12 months follow-up	no data available		-	(0 RCTs)	-
tolerability - total number of adverse events	escitalopram (n = 459) vs. placebo (n = 389): post-intervention; melatonin (n = 29) vs. placebo (n = 15): post-intervention; sertraline (n = 181) vs. placebo (n = 206): post-intervention		-	(5 RCTs)	⊕⊝⊝⊝ VERY LOW [2 4 5 9 10]
acceptability - drop-outs due to adverse events: post-intervention	Study population		OR 2.05 (1.07 to 3.89)	561 (5 RCTs)	⊕⊝⊝⊝ VERY LOW [2 4 10 11]
	58 per 1.000	111 per 1.000 (61 to 192)			

acceptability - drop-outs due to any cause: post-intervention	Study population		OR 1.13 (0.73 to 1.73)	962 (9 RCTs)	⊕⊖⊖⊖ VERY LOW [2 4 5 10 12]
	226 per 1.000	248 per 1.000 (176 to 336)			
acceptability - drop-outs due to any cause: 6-12 months	Study population		OR 1.13 (0.69 to 1.86)	327 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [2 4 5 10 12]
	274 per 1.000	299 per 1.000 (207 to 413)			

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once due to indirectness. Due to the nature of this review, we included all types of chronic physical illnesses. With five out of ten studies including patients after stroke, they weighted heavily in the meta-analyses. Therefore, there is some uncertainty with the applicability of the effect to all types of diseases.

[2] Publication bias strongly suspected.

[3] The low and high risk values are the two extreme numbers of incidences in the control groups from studies included in the review.

[4] Downgraded twice due to imprecision. For one or more studies there were only small sample sizes, only few events, and/or wide confidence intervals.

[5] Downgraded twice due to risk of bias. Across all included trials, outcome data was incomplete, and bias for selective reporting was either high or unclear. One study was insufficiently blinded, and one study had a high risk for other bias.

[6] Downgraded once due to indirectness. Due to the nature of this review, we included all types of chronic physical illnesses. With only one study on the short-term effect, there is some uncertainty with the applicability of the effect to all types of diseases.

[7] Downgraded once due to indirectness. Due to the nature of this review, we included all types of chronic physical illnesses. With two out of three studies including patients after stroke, they weighted heavily in the meta-analyses. Therefore, there is some uncertainty with the applicability of the effect to all types of diseases.

[8] Downgraded once due to inconsistency. One study favoured controls.

[9] Downgraded twice due to inconsistency across studies. For SSRIs, two studies report more adverse events in the escitalopram group than the placebo group, while another two studies report fewer adverse events in the sertraline group than the placebo group.

[10] Downgraded once due to indirectness. Due to the nature of this review, we included all types of pharmacological interventions. With seven studies including SSRIs, there is some uncertainty with the applicability on other classes of antidepressants.

[11] Downgraded twice due to risk of bias. Outcome data was incomplete and reporting bias was either high or unclear.

[12] Downgraded twice due to inconsistency across studies with one study favouring the pharmacological intervention.

BACKGROUND

Description of the condition

Major depressive disorder is characterised by an array of symptoms including depressed mood, loss of interest or pleasure, diminished energy, fatigue, difficulties with concentration, changes in appetite and sleep disturbances (APA 2013). Depression is a common condition with a lifetime prevalence of 16% (Kessler 2003), and a 12-month prevalence rate between 6% and 10% (Baumeister 2007).The World Health Organisation (WHO) rated depression as the third leading contributor to the burden of disease worldwide (and predicted it to become the first in 2030), accounting for more than 4% of total disability-adjusted life-years (DALYs) (WHO 2008).

There is strong evidence for even higher rates of depression in adults with long-term physical conditions (also termed medical illness or chronic illness) compared to those without it (Gunn 2012; Härter 2007a; Holahan 2010; Patten 2001). Research has not yet established a causal link between depression and long-term physical conditions, but shows a distinctive decline in health when depression is present (WHO 2007). The presence of depression in adults with long-term physical conditions is associated with a negative prognosis in terms of increased morbidity and mortality rates (Katon 2003; Katon 2007), increased health care costs (Baumeister 2012a; Haschke 2012; Hutter 2010; Hutter 2011; Katon 2002), decreased adherence to treatment regimens (Evans 2005), and a substantial loss in quality of life (Baumeister 2011a).

While negative effects of depression are apparent, its origins remain yet inconclusive. When long-term physical conditions precede a depressive episode, as it is the case in prevention trials, depression can be categorised by its assumed main cause or trigger.

- It might be caused by the treatment of the illness (i.e. substance-induced depression).
- It might directly result from the illness (i.e. organic depression).
- It could be a psychological response of coping with the illness (DGPPN 2012; Freedland 2010; Härter 2007b).
- It might possess a common disposition with the illness (i.e. genetic pleiotropy, common socio-economic and demographic characteristics) (de Geus 2006; McCaffery 2006).
- It might co-occur with the illness due to chance.

Therefore, depression subtypes need to be considered within the context of the interplay between diatheses and stress, as the principal underlying determinants of depression (Baumeister 2012b; Durand 2012). Among adults with long-term physical conditions, a variety of factors such as worsening condition, unrelieved pain, functional impairment, or social isolation are associated with the possible onset of depression (Clarke 2009). Therefore, these adults are a selected population with an increased risk to (newly) develop depression (Gunn 2012; Härter 2007a; Holahan 2010; Patten 2001). This risk for depression implies the potential benefit of primary prevention trials.

Description of the intervention

To gain a comprehensive understanding of the term prevention as we applied it throughout this review, some considerations have to be taken into account. First of all, prevention needs to be defined. The current body of literature concerning prevention of depression in adults with long-term physical conditions is considerable, but often lacks clear definition and conceptualisation. Prevention is usually subdivided into primary, secondary and tertiary prevention. While these terms are commonly used, reports and studies often lack explicit operationalisation (Muñoz 1996).

To prevent something, an intervention must take place before the event occurs; in this case, to prevent depression, the preventive intervention must take place before the onset of first depressive symptoms. This is the case only in primary prevention trials. In contrast, secondary prevention of depression seeks to prevent the progression of a disease or disorder by early detection and treatment of the condition, and is therefore considered to be a 'treatment' rather than an actual type of prevention. Tertiary prevention of depression includes interventions aiming to prevent relapse and recurrences of depressive disorders and was reinstated to be considered as 'maintenance' of the condition (Mrazek 1994; O'Connell 2009).

The Institute of Medicine's report on *Reducing Risks for Mental Disorders* considers only primary prevention strategies as 'prevention' *stricto senso* (Muñoz 1996). The type of prevention, the population to which it is applied, and the balance of benefits against risk (adverse events) and cost (cost-effectiveness, cost-utility) determine the specificity of a primary preventive intervention (Gordon 1983). Therefore, it can be specified as either universal, selective or indicated. While universal prevention aims at the population as a whole, selective and indicated prevention are applied to subgroups of the population whose risk is above average (selective prevention) or who show subthreshold symptoms and/or exhibit risk factors such as biological markers (indicated prevention) (Gordon 1983). While the latter might easily be confused with secondary prevention or treatment, the National Institutes of Health (NIH) argue that a clinical abnormality is distinct from a clinical symptom, and that the treatment of such an abnormality serves to prevent the development of some later symptoms. Hence, indicated prevention is different from treatment (Gordon 1983).

All the same, up to 80% of adults with depression experience at least one recurring episode (Wittchen 2010), implying a great likelihood of a history of depression sometime in their lives. Therefore, adults included in depression prevention trials might match the requirements of tertiary prevention rather than those of primary prevention. The main intent of tertiary prevention, however, differs from primary prevention: while primary prevention aims at preventing the onset of depression, tertiary prevention deals with the aftermath of a depressive episode that might still be present, is about to subside, or has recently dissolved.

With regard to types of preventive interventions, two approaches might be considered that have been shown to be effective for the treatment of depression in adults with long-term physical conditions. These are psychological interventions (Baumeister 2011b; Baumeister 2012c; Beltman 2010; Stockton 2004) and pharmacological interventions (Baumeister 2011b; Baumeister 2012c; Gill 2000; Krishnan 2005; Rayner 2010; Simon 2005). There is evidence that the onset of depression in general can be prevented or at least be delayed by psychological interventions (Cuijpers 2008). As for pharmacological interventions, there are hints that prophylactic treatment with antidepressants can decrease the incidence of depression in adults with head and neck cancer (Lydiatt 2013).

There is a multitude of psychological interventions such as cognitive behavioural therapy, psychodynamic therapies, behaviour therapy or behaviour modification, systemic therapies, third wave cognitive behavioural therapies, humanistic therapies, or integrative therapies. All interventions are carried out by a healthcare professional in a setting of individual, group, family or couples therapy. Psychological interventions aim to recognise, improve or prevent distress by direct or interactive communication.

Complementary, pharmacological interventions are commonly used in the treatment of depression. Selection of antidepressant drugs depends on the type of depressive disorder, adverse reactions and present co-morbidities (both psychological and physical). Most prevalent classes of antidepressants are tricyclic antidepressants, heterocyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors (MAOIs).

How the intervention might work

The majority of psychological therapies are based on social-learning, biosocial, and psychodynamic theories, hypothesising that impairments might be learned, or by assuming an interaction of given dispositions (also called vulnerabilities) and circumstantial influences. They comprise various approaches targeting and altering unhelpful emotions, behaviours and/or cognitions to alleviate depressive symptoms. A number of Cochrane Reviews address the effectiveness of psychological interventions. Even though the certainty of evidence is mainly low to moderate, evidence suggests an effective treatment of depression by means of psychological interventions in adults as well as in the physically ill (Akechi 2008; Baumeister 2012c; Shinohara 2013; Thomas 2006; Whalley 2011).

The majority of pharmacological interventions target monoamine neurotransmitter function, and were assumed to convey their antidepressant effects by enhancement of functional activity of serotonin, noradrenaline and/or dopamine. However, more frequent research approaches challenge a "purely neurotransmitter-based explanation for antidepressant drug action" (Harmer 2017). At present, it is not yet known exactly how antidepressants exert their effects. Various theories have been put forward, including the neuroplasticity and the neuropsychological theory. Instead of a simple neurochemical understanding, novel theories include a broader understanding of antidepressant drug action by considering the effects of antidepressants on emotional and cognitive function as well as neuroplasticity (Harmer 2017). Several Cochrane Reviews investigate the potential effects of antidepressants, suggesting a beneficial effect of pharmacological treatment for depression (Arroll 2009; Cipriani 2009; Cipriani 2012; van Marvijk 2012). This also appears to be the case in adults with long-term physical conditions (Gill 2000; Rayner 2010).

While the importance of managing adverse events is emphasised for all antidepressant treatments, including both psychological and pharmacological interventions, special attention has to be given to adults with long-term physical conditions. Especially for pharmacological agents, the potential benefits of antidepressants need to be balanced against their potential side effects and the challenges of managing the complex drug regimens of adults with multiple morbidities. Despite this, clinical guidelines recommend psychological interventions for the treatment of subthreshold to moderate depression, and pharmacological interventions for the treatment of moderate to severe depression in adults with long-term physical conditions (NICE 2009).

The effective treatment of depression by means of psychological as well as pharmacological interventions implies that they may also be beneficial in the use of these treatments as preventive interventions.

Why it is important to do this review

Co-morbid depression in adults with long-term physical conditions leads to increased symptom burden and medical complications (Evans 2005; Katon 2003; Katon 2007; WHO 2008). It has a considerable effect on health care utilisation and cost, and is associated with substantial suffering (Baumeister 2011a; Baumeister 2012a; Haschke 2012; Hutter 2010; Hutter 2011; Katon 2002). There is evidence from several Cochrane Reviews that depression in adults with long-term physical conditions can be treated; however, the effectiveness of interventions for manifest depression seems to be limited (Baumeister 2011b; Baumeister 2012c; Gill 2000; Rayner 2010). Thus, the scientific and healthcare implications of preventing depression as a potentially effective and cost-effective way of dealing with potential depression in adults with long-term physical conditions would be substantial.

This review gives an overview of available prevention trials for depression in adults with long-term physical conditions, and offers conclusions on the effects of prevention. We examined different types of interventions (psychological and pharmacological), allowing us to draw conclusions about specific preventive interventions. We define prevention in this review as being either primary (prevention of first onset of depression) or tertiary (prevention of recurrent depression), and exclude secondary prevention and (tertiary) relapse prevention.

Furthermore, follow-up data and sources of heterogeneity are explored and may help to provide suggestions for the design of future studies. We discuss methodological limitations, problems and shortcomings, which may also help to guide future research. To allow the integration of new evidence and findings, we will continuously maintain and update this review.

According to diagnostic criteria defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), a 'substance-induced mood disorder' is characterised by the same symptoms as major depression with the exception that the source of the symptoms is clearly attributed to pharmacological agents (APA 2000). Certain long-term physical conditions such as cancers, viral diseases, or multiple sclerosis are commonly treated with agents that are considered to cause or convey depressive symptoms (Raison 2005; Wichers 2005). While adults receiving such agents might also benefit from preventive interventions, substance-induced depression is clearly distinct from depression in adults with long-term physical conditions, and will therefore be treated separately in a complementary review.

O B J E C T I V E S

To assess the effectiveness, acceptability and tolerability of psychological or pharmacological interventions in comparison to controls in preventing the incidence of depression in adults with long-term physical conditions, either before first ever onset of depressive symptoms (i.e. primary prevention) or before first onset

of depressive symptoms in patients with a history of depression (i.e. tertiary depression). Specifically we aimed to determine:

1. the effects of preventive psychological interventions; and
2. the effects of pharmacological interventions.

METHODS

Criteria for considering studies for this review

Types of studies

We restricted eligible study designs to randomised controlled trials (RCTs), cluster-RCTs, and cross-over trials. We included trials published in any language and with any publication status. We had no restriction on sample size or duration of follow-up.

Types of participants

Participant characteristics

Adult participants (age 18 years or older) of either sex were eligible for inclusion.

Diagnosis

We included trials if participants had at least one diagnosed long-term physical condition meeting International Classification of Diseases (ICD)-10 criteria (WHO 1992), and no major depressive disorder at baseline. To confirm the absence of depression at baseline, and to determine the onset of depression in the course of the trial, depression had to be diagnosed by means of a standardised clinical interview, using ICD or DSM criteria. However, in favour of providing a more comprehensive review, we also included trials using validated self-reports, or rating scales with specific cut-off points for depression, or a medical diagnosis made by a healthcare professional. For a full list of included long-term physical conditions please see Appendix 1.

Co-morbidities

Due to the nature of this review, participants with one or more co-morbid physical or mental disorders, other than depression were eligible for inclusion.

Settings

We included trials regardless of the setting (including inpatients and outpatients). Participants might have been treated in acute care hospitals, emergency facilities, general practice, rehabilitation settings, or extended care facilities such as nursing homes or communities.

Subset data

In case of mixed study samples (e.g. a sample of participants who were initially without depression or anxiety; a sample consisting of participants who were mainly with a long-term physical condition), we planned to obtain 'clear' data of interest from study authors. If data could not be obtained, or if the use of a subsample would break the RCT, we planned to exclude the study.

Types of interventions

Experimental interventions

The following psychological and pharmacological preventive interventions specifically targeting depression were eligible for inclusion:

1. Psychological interventions:
   a. cognitive behavioural therapy, i.e. problem solving, stress management, restructuring;
   b. psychodynamic psychotherapy, i.e. psychoanalytic therapy, countertransference, insight oriented therapy;
   c. behaviour therapy or behaviour modification, i.e. activity scheduling, exposure therapy, social skills training;
   d. systemic therapy, i.e. conjoint therapy (couple, family), narrative therapy, socio-environmental therapy;
   e. third wave cognitive behavioural therapies, i.e. mindfulness-based cognitive therapy, behavioural activation, dialectical behaviour therapy, acceptance and commitment therapy;
   f. humanistic therapies, i.e. Rogerian, expressive therapy, supportive therapy;
   g. integrative therapies, i.e. interpersonal therapy, counselling, cognitive analytical therapy;
   h. other psychological-oriented interventions, i.e. catharsis, drama therapy, bibliotherapy.
2. Pharmacological interventions:
   a. tricyclic antidepressants, i.e. amitriptyline, desipramine, imipramine, clomipramine;
   b. heterocyclic antidepressants, i.e. mianserin, trazodone, amoxapine, maprotiline;
   c. SSRIs, i.e. citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline;
   d. MAOIs, i.e. irreversible: phenelzine, tranylcypromine; reversible: brofaromine, moclobemide;
   e. other antidepressants, i.e. serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, milnacipran; noradrenergic and specific serotonergic antidepressants such as mirtazapine; or unclassified antidepressants such as agomelatine.

Comparator interventions

In the case of psychological prevention trials, the comparison group had to be 'treatment as usual' (TAU), 'waiting list,' 'attention placebo' (which is regarded as inactive by both researchers and participants), or 'psychological placebo' (which is regarded as active by participants and inactive by researchers).

In case of pharmacological prevention trials the comparison group had to be 'placebo.'

Excluded interventions

1. Secondary preventive interventions seeking to prevent the progression of a disease or disorder by early detection and treatment of the condition (which marked it a 'treatment' rather than an actual prevention)
2. Tertiary prevention that aimed to prevent relapse, to maintain an aspired condition, or to implement rehabilitation services (including continuation therapy)

3. Health promotion interventions designed to improve health and well-being

Types of outcome measures

Primary outcomes

The primary outcomes were incidence of depression following the preventive intervention, as well as tolerability and acceptability of the preventive intervention.

1. Incidence of depression: depression was defined by meeting the criteria of major depression set out by DSM (DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994), DSM-IV-TR (APA 2000); DSM-V (APA 2013)), or the criteria of a depressive episode set out by ICD (ICD-9 (WHO 1978), ICD-10 (WHO 1992)). Depression had to be measured or assessed by standardised interviews (such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First 1996), Composite International Diagnostic Interview (CIDI) (WHO 1990), Mini-International Neuropsychiatric Interview (MINI) (Sheehan 1998), or Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing 1990)), or treating physician.
2. Tolerability and acceptability: adverse events (harms, side-effects) and drop-outs during preventive intervention were a proxy measure for preventive intervention tolerability and acceptability.
   a. total number of adverse events experienced;
   b. drop-outs due to adverse events; and
   c. drop-outs due to any cause.

Secondary outcomes

1. Incidence of depression, measured by
   a. scoring above the cut-off for depressive disorder as defined by symptom scores on standardised, validated rating scales (such as the Hamilton Rating Scale for Depression (HDRS/HAMD/HAM-D) (Hamilton 1960), or the Montgomery-Åsberg Depression Scale (MADS) (Montgomery 1979), or
   b. scoring above the cut-off for depressive disorder as defined by symptom scores on standardised, validated self-report questionnaires (such as the Beck Depression Inventory (BDI) (Beck 1961), the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff 1977), the Hospital Anxiety and Depression Rating Scale (HADS) (Zigmond 1983), or the Patient Health Questionnaire - depression module (PHQ-9) (Kroenke 2001).
2. Severity of depression (measured by self-report questionnaires or rating scales such as BDI, HDRS, HADS, or MADS)
3. Cost-effectiveness (measured by the incremental cost-effectiveness ratio (ICER)
4. Cost-utility (measured by quality-adjusted life years (QALYs))

Hierarchy of outcome measures

Due to the great likelihood of more than one reported eligible outcome, we included data as follows.

1. In case of available data from both rating scales and self-report questionnaires, data from rating scales were prioritised.
2. In case of several outcome measures of the same hierarchy level used in one study, we selected the outcome measure most frequently used across all studies. Therefore, availability

were to determine the selection of the outcome measure (e.g. if four studies report data from the Hamilton Rating Scale for Depression and two studies from the Montgomery-Åsberg Depression Scale, Hamilton Rating Scale for Depression were to be selected).

3. In case of several outcome measures of the same hierarchy level and the same availability across studies, the outcome measure was to be randomly selected.

Further, if different studies were to use the same outcome measure but still use different cut-off scores, we were to conduct sensitivity analysis to account for this (see Sensitivity analysis).

Timing of outcome assessment

Due to the nature of this review, we encountered multiple observations and heterogeneity concerning the follow-up length of the outcome assessment. We analysed follow-up durations using different time frames:

1. short term (less than six months post-intervention);
2. medium term (six to 12 months post-intervention); and
3. long term (more than 12 months post-intervention).

In case that studies reported more than one assessment per period, we included the assessment that covered a greater period (e.g. we prioritised the assessment at three months over that at two months).

We conducted corresponding sensitivity analysis to evaluate the sustainability of possible antidepressant effects of preventive interventions (follow-up; post-randomisation instead of post-intervention).

Search methods for identification of studies

The searches relied to a large extent on the use of subject headings and indexing terms (e.g. the US National Library of Medicine's 'Medical Subject Headings' (MeSH), Embase's 'Emtree' and the American Psychological Asssociation's 'APA Thesaurus'), as creating a fully comprehensive and sensitive list of keywords (including synonyms, related terms, variant spellings) for 'all physical illness' was unfeasible. The list of keywords was created in collaboration with the review authors and Cochrane Common Mental Disorders (CCMD) Information Specialist, using the ICD-10 list (Appendix 1) and relevant guidelines (NICE 2009) and reviews (AHRQ 2012) as a source of reference for co-morbid health conditions associated with depression.

Electronic searches

Searches were first conducted in November 2014, with updates in November 2017 and February 2020. The information specialist with CCMD searched the following databases:

- Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR) (all available years) (Appendix 2)
- The Cochrane Library (all issues, to Issue 2, 2020);
- Ovid MEDLINE databases (1 January 2005 to 6 February 2020);
- Ovid EMBASE (1 January 2011 to 6 Feb 2020);
- Ovid PsycINFO (all years, to 9 Feb 2020).

The additional biomedical database searches (Appendix 3) were performed to identify RCTs beyond the scope of the CCMDCTR, due

to the inclusion criteria of this review (i.e. adults diagnosed with at least one long-term physical condition with no depression at baseline). The CCMDCTR also fell out of date during the course of this review.

A date restriction was applied to the MEDLINE and Embase searches, as records from these databases have already been screened for inclusion in CENTRAL (Lefebvre 2008). For further details, see the CENTRAL help file, available on the Cochrane Library website.

No further date restrictions were applied to the search.

International trial registries

Two international trial registries, ClinicalTrials.gov at the US National Institutes of Health, and the WHO International Clinical Trials Registry Portal (ICTRP), were searched to identify additional ongoing or unpublished studies.

Searching other resources

Reference lists

We searched references of included studies for relevant publications and cited unpublished trials. Furthermore, we checked relevant reviews and those articles that cited the studies we intended to include.

Data collection and analysis

Selection of studies

Based on the information gained from title and abstract, two authors (HK, OM) independently assessed all identified studies for the inclusion criteria, using the systematic review web application Rayyan (https://rayyan.qcri.org/welcome). If there was sufficient information for exclusion, the study was rejected. In the second step, the two authors independently accessed the full text of the potentially eligible results and compiled a list of studies that they believed met inclusion criteria. The two lists were compared and discrepancies discussed. Any further disagreements were resolved by involving a third review author (HB). We recorded the selection process in sufficient detail to complete a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1) and a 'Characteristics of excluded studies' table.

Figure 1. Study flow diagram.

SEARCH PROCESS 1:
CCDAN registers

CCDANCTR-Studies &
CCDANCTR-Reference

Total = 2,897 refs

SEARCH PROCESS 2: Other databases

Ovid MEDLINE = 3,257 refs

Ovid PsycINFO = 2,867 refs

Ovid EMBASE (non-MEDLINE) = 679 refs

CENTRAL = 3,848 refs

Total = 10,651 refs

SEARCH PROCESS 3: Additional resources

CDSR, DARE (Reviews) = 246 refs

Reference Lists = 8 refs

Total = 254 refs

Identification:
Total = 13,802 refs

Dublicates removed:
Total = 4,275 refs

SCREENING: no. of records screened after de-duplication
Total = 9,527 refs

Records excluded:
Total = 9,398 refs

Records excluded, with reasons:

Full-text = 85 refs

- participants recruited on basis of depressive symptoms (depression at baseline) = 33 refs
- incidence of depression was no (primary)outcome, or the intervention did not specifically address depression = 27 refs
- indicative/selective prevention = 6
- patients with antidepressant treatment at baseline included = 5
- mixed study sample = 4
- no suitable control group = 4
- no RCT = 3
- no long-term physical condition = 1
- no validated measures = 1
- data not accessible = 1

Trials = 8 refs
Comments = 8 comments

Total = 101 refs

ELIGIBILITY: no. of articles assessed

- Full-text articles = 100 refs
- Protocols = 6 refs
- Trial registrations = 13 refs
- Comments = 8 refs
- Corrections = 2 refs

Total = 129 refs

INCLUDED REFERENCES: no. of records included

- primary full texts = 11 refs
- secondary full texts = 8 refs
- protocols = 2 refs
- corrections = 2 refs
- trials = 5 refs

Figure 1.   (Continued)

- corrections = 2 refs
- trials = 5 refs

Total = 28 refs

INCLUDED STUDIES: no. of studies included

Total = 11 studies

Number of studies included in quantitative synthesis (meta-analysis)

Total = 10 studies

Update Search February 2020

SCREENING: no. of records screened after de-duplication

Total = 2,314 refs

Records excluded:

Total = 2,288 refs

Records excluded, with reasons

Full-text = 15 refs

- participants recruited on basis of depressive symptoms (depression at baseline) = 9 refs
- no long-term physical condition = 2 refs
- incidence of depression was no (primary)outcome, or the intervention did not specifically address depression = 2 refs
- patients with antidepressant treatment at baseline included = 1 ref
- age criteria not fulfilled = 1 ref

Protocols = 3 refs
Conference papers = 8 refs

Total = 26 refs

ELIGIBILITY: no. of articles assessed

- Full-text articles = 15 refs
- Protocols = 3 refs
- Conference papers = 8 refs

Total = 26 refs

INCLUDED STUDIES: no. of additional studies included after the update search

Total = 0 studies

Data extraction and management

Two review authors (HK, OM) independently extracted data. All data was cross-checked for completeness by also including a research assistant. After discussing and resolving any disagreements by involving a third review author (HB), we entered data in the Cochrane Collaboration statistical software, RevMan 5 (Review Manager 2014). In case of missing data or information, we attempted to contact the trial's primary investigators.

We collected the following data and information from each included study report.

- Description of trial: authors, year of publication, funding.
- Study population: type of physical illness, sample size (numbers randomised, numbers treated, numbers at follow-up), social demography, medical records (including history of depression if available).
- Diagnostic and assessment of depression: physician's diagnosis (in accordance to DSM or ICD), standardised diagnostic interview, self-report questionnaire (including cut-off scores).
- Types of intervention:
  - intervention group: psychological, pharmacological, other (type, dose, duration, methods of delivery);
  - control group: placebo, usual care, waiting list, attention placebo.
- Research design: sampling, randomization, follow-up.
- Outcome measures: description of primary and secondary measures, drop outs, adverse events.
- Statistics: sample sizes, incidence, means, standard deviation/error, and P values.

Main comparisons

We evaluated the effects of the preventive psychological and pharmacological interventions separately as below:

1. psychological interventions versus usual care, waiting list, attention placebo, or no intervention;
2. pharmacological intervention versus placebo.

Furthermore, we planned to conduct subgroup analyses for different types of long-term physical conditions and classes of antidepressants. This was not possible due to lack of data. We also planned to conduct subgroup analyses for types of psychological interventions but this was not possible as we included only one such trial.

Assessment of risk of bias in included studies

Using the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011), two authors (HK, OM) independently assessed the risk of bias for all eligible studies. We discussed any disagreements, and sought further advice from a third review author (HB).

We provide 'Risk of bias' tables which present the domain, the review author's judgement and support for such judgement.

We considered the following domains for risk of bias:

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was allocation adequately concealed?
3. Blinding of participants and personnel: was knowledge of the allocated intervention adequately prevented during the study?
4. Blinding of outcome assessors: was knowledge of the allocated intervention adequately prevented during the study?
5. Incomplete outcome data: were incomplete outcome data adequately addressed?
6. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?

7. Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias?

The support of judgement ensured transparency by providing a description from which judgements of risk of bias can be made. Furthermore, we present the review author's judgement on the obtained data. Within and across studies risk of bias was judged to be low, unclear or high for each domain.

We provide a description and graphic presentation of all risk of bias data.

Measures of treatment effect

Dichotomous data

For dichotomous data, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) to assess the incidence of depression.

Continuous data

For continuous data, we calculated standardised mean differences (SMDs) with 95% CIs to assess depression severity across different depression scales. We used Hedges' adjusted g statistic to calculate SMDs (it is very similar to Cohen's d statistic, but includes an adjustment for small sample bias). For a descriptive assessment of tolerability (adverse events) and acceptability (drop-outs), we provide percentages that might offer estimates for these effects.

Unit of analysis issues

Studies with multiple treatment groups

Multiple-arm studies contain more than two (intervention, comparison) relevant treatment arms (in addition to the control group there might be different types of interventions or different doses of medication). We avoided any possible bias caused by multiple comparisons with one control group by combining the groups to create a single pair-wise comparison (Higgins 2011).

Cluster-randomised trials

We intended to include cluster-randomised trials if the study had been adjusted for the effect of the clustering, or an estimate of the intraclass correlation coefficient (ICC) could be obtained to adjust for the effect of the clustering (missing data was to be requested from authors). If the ICC were not to be acquired from study authors, external estimates were to be obtained from similar studies (Higgins 2011). If no estimate at all would have been available, we were to exclude the trial from analysis. However, no cluster-randomised trials were included in this review.

Cross-over trials

Results of cross-over trials might be influenced by a carry-over effect. Here, a treatment in the first randomised treatment period has an effect that carries over to the second randomised treatment period. We also considered cross-over designs eligible for inclusion but no cross-over trials were identified. If we identify any cross-over trials in future updates of this review, we will include only data from the first randomised treatment period.

Dealing with missing data

In keeping with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we dealt with missing data as follows.

- We collected and documented information on missing data. Whenever possible, we contacted the original study authors to obtain relevant missing data. We documented all correspondence with authors, and reported which authors responded and what methods they (might) have used for imputing data (such as multiple imputations).
- When data can be assumed to be 'missing at random' (due to available information), we were to analyse only the available data.
- Study drop-outs were considered to be 'not missing at random'. We assumed that adverse events might arise due to the treatment or the development of depressive symptoms, and therefore, might pose the major reasons for discontinuation of study participation. To account for this, we conducted per protocol (PP) analyses instead of intention-to-treat (ITT) analyses. Therefore, incidence of depression is reported as the ratio of 'n incidence' to ('n randomised' minus 'n drop-outs').
- We performed sensitivity analyses to assess the impact of missing data.

Assessment of heterogeneity

To identify statistical heterogeneity, we visually evaluated the forest plots and assessed Chi^2 test of heterogeneity. Given the low power of the Chi^2 test when trials are small, we used a significance level of α = 0.10 (Higgins 2011).

In addition, we used the I^2 heterogeneity statistic to quantify inconsistency across studies to assess the impact of heterogeneity (Higgins 2003). We interpreted I^2 values in accordance with the *Cochrane Handbook* (Higgins 2011). A rough guide to interpretation is as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

In order to minimise publication bias, we tried to identify unpublished data and included studies published in any language. With more than ten studies included, we graphically examined the risk of existing publication bias by the use of a funnel plot (Higgins 2011). The limitations of funnel plots (asymmetry does not necessarily imply publication bias or publication bias might exist even though there is no asymmetry) were taken into consideration (Guyatt 2011).

Furthermore, we identified outcome reporting bias by comparing planned and reported outcomes. We identified missing outcome data, tried to obtain it by contacting authors, and in case of its unavailability reported its absence.

Data synthesis

Our decision on whether or not we should perform meta-analyses was based on the assessment of clinical, methodological and statistical heterogeneity:

1. use of a fixed-effect model, where we would expect the included trials to estimate the same true value;

2. use of a random-effects model, for which we expect the included trials to estimate different but related estimates of effect; or
3. no meta-analysis, in which case we expect the included trials to estimate different and unrelated estimates of effect.

We used a random-effects model.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses are observational by nature and often involve multiple analyses which increase the likelihood of falsely positive results. They should be interpreted with caution.

We planned to conduct the following subgroup analyses:

1. Type of long-term physical condition: we expected differences in the efficiency, acceptability and tolerability of the preventive intervention depending on the type of long-term physical condition (subgroup analyses were to be conducted for type of long-term physical conditions if three or more studies deal with one specific disease as listed in Appendix 1);
2. Type of psychological intervention: we expected differences in the efficiency, acceptability and tolerability of the psychological intervention depending on the type of psychological interventions (subgroup analyses were to be conducted for the type of psychological intervention if three or more studies deal with on specific psychological intervention);
3. Class of antidepressant: we expected differences in the efficiency, acceptability and tolerability of the pharmacological intervention depending on the class of antidepressant (subgroup analyses were to be conducted for the type of pharmacological intervention if three or more studies deal with one specific pharmacological intervention).

Sensitivity analysis

In order to examine the robustness of the results of the primary outcome, we intended to perform the following sensitivity analyses:

1. Assessment method: different studies might use the same outcome measure but still use different cut-off scores to separate depressed from non-depressed participants; we were to exclude studies using low cut-off scores and describe the procedure in detail.
2. Quality of studies: we excluded those studies which posed a high risk of bias and might therefore affect the quality of study results; sensitivity analyses were to be conducted for studies who:
   a. fail to double blind (participants and treating health care professional) in case of pharmacological and other interventions (psychological interventions are not expected to blind participants);
   b. lack proper allocation concealment;
   c. might show an impact of missing data: in accordance with the *Cochrane Handbook* (Higgins 2011), we were to conduct 'best case' and 'worst case' analyses to evaluate the impact of participants who were lost to follow-up, specifically:
      i. best case scenario: all missing data in the control group were to be considered as occurrence of depressive symptoms;
      ii. worst case scenario: all missing data in the treatment group were to be considered as occurrence of depressive symptoms;

d. were cluster-randomised trials.

3. Selection of participants: we were to exclude those studies which only include selected samples of participants at higher risk for depression, e.g. studies which might:
   a. include all participants in a diagnostic group;
   b. apply eligibility criteria (such as history of depression) which might single out participants at even higher risk for depression; or
   c. enrol only participants who score above a threshold on a self-report questionnaire (i.e. subthreshold depression), but do not yet meet criteria for mild depression (which might also mark them at being at even higher risk for depression).

4. Length of treatment: we conducted analyses where follow-up was post-randomisation instead of post-intervention. We analysed follow-up durations using different time frames:
   a. short-term (less than six months post-randomisation);
   b. medium-term (six to 12 months post-randomisation); and
   c. long-term (more than 12 months post-randomisation).

5. Type of funding: we excluded studies based on commercial funding, as they might have posed a bias towards the sponsors' interests.

Summary of findings and assessment of the certainty of the evidence

We summarised key findings of our review in 'Summary of findings' tables (Higgins 2011). The tables include the primary outcomes the incidence of depression, acceptability and tolerability for both psychological (Summary of findings 1) and pharmacological (Summary of findings 2) preventive interventions. We assessed the certainty of the body of evidence for each outcome with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schünemann 2013). The 'Summary of findings' tables include numbers of studies and participants, ORs or SMDs respectively, as well as an estimation of the certainty of the evidence based on the standards of GRADE. Certainty of evidence was assessed considering the risk of bias of included studies, unexplained heterogeneity (inconsistency), the directness of the evidence (indirectness), preciseness of results (imprecision), as well as the risk of publication bias (other considerations).

R E S U L T S

Description of studies

Results of the search

After de-duplication, the systematic search yielded 9,527 references. Two review authors (HK, OM) screened the results, excluding 9,398 references. Among these, two studies are still ongoing and recruiting (ACTRN12616000886482; Madsen 2017; see also Characteristics of ongoing studies). A total of 13 studies are still awaiting classification (see Characteristics of studies awaiting classification). Among these, two studies have completed data collection but results are not published yet (ChiCTR-TRC-12003489; Sander 2017). For three references, no corresponding study or further data could be identified (EudraCT-2005-005266-37; Guneri 2006; van Zyl 2006). Another eight studies were reported in Chinese and could not be accessed (He 2004; Li 2004; Lu 2010; Wen 2006; Xu 2006; Zhong 2013; Zhou 2008; Zhu 2014). Of the 129 full-text articles assessed for eligibility, 101 references were excluded. These comprised 85 full-texts, eight trial registrations, and eight

comments. Among the excluded studies, 20 studies (Almeida 2010; Beglinger 2014; Brody 2005; Browne 2013; Burns 2007; Couch 1976; Dean 1969; de Jonge 2009; Hackett 2010; Hackett 2013; Karp 2016; Kong 2007; Mossey 1996; Niedermaier 2004; Pitceathly 2009; Pols 2017; Rovner 2014; van der Aa 2015; Yeung 2014; Zhang 2013) comprising 26 references were excluded for less obvious reasons than not fulfilling inclusion criteria such as 'Types of studies,' 'Types of participants,' or 'Types of interventions.' Reasons for excluding these studies are in the Characteristics of excluded studies. Any discrepancies in assessment were resolved by involving another review author (HB).

Finally, we included 28 references addressing 11 different trials (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rasmussen 2003; Robinson 2008; Rovner 2007; Tsai 2011; see also Characteristics of included studies). Figure 1 offers a detailed overview of the study selection process in form of a PRISMA flow diagram.

In February 2020, we did an update of the systematic search, yielding a further 2,326 references. Handsearches yielded another six references. After de-duplication, 2,314 references were once again screened by two of the review authors (HK, OM). 2,288 references were excluded after screening (among these one study (comprising two conference papers) was already included in prior search batches (Hansen 2012) and was not included again). Of the 26 full-texts assessed for eligibility, 26 references were excluded (comprising 12 trials reported in 15 references, three protocols, and eight conference papers). Among the excluded studies, 4 studies (Borrelli 2019; Hood 2018; Kredentser 2018; Read 2020) comprising 4 references were excluded for less obvious reasons than not fulfilling inclusion criteria such as 'Types of studies,' 'Types of participants,' or 'Types of interventions. Therefore, no additional studies were included after the February 2020 update.

Included studies

Design

All 11 included studies were RCTs. Of the 11 included trials, ten compared pharmacological interventions to placebo, and were included in the final meta-analyses (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rasmussen 2003; Robinson 2008; Tsai 2011). Given that only one trial compared psychological interventions to a fitting control condition, pooling of results was not possible (Rovner 2007). Due to the nature of the study design, the psychological intervention was single-blinded. Two trials included a three-arm parallel randomised controlled clinical trial design with Robinson 2008 comparing a pharmacological and a psychological intervention (problem-solving therapy) to placebo, and Narushima 2002 comparing two different types of a pharmacological intervention (fluoxetine, nortriptyline) to placebo. For Robinson 2008 we only included the pharmacological intervention because their comparison of a psychological intervention to placebo was not eligible for inclusion. As for Narushima 2002, we combined the two groups of pharmacological interventions (i.e. fluoxetine/nortriptyline) to create a single pair-wise comparison. For details of the included trials, see Characteristics of included studies.

We found no eligible cluster-randomised trials or cross-over trials.

Sample sizes

Sample sizes of randomised participants varied from 36 participants (Lydiatt 2008) to 239 participants (Hansen 2012). In total, 1279 participants were randomised. Among these, 653 participants were included in the intervention groups, and 626 participants in the control groups. Due to drop-outs, we analysed the data of 1031 participants. For the comparisons of pharmacological interventions to placebo, we analysed data of 837 participants, among these 423 participants in the intervention groups, and 414 participants in the control groups. For the comparison of a psychological intervention to TAU we analysed data of 194 participants, 95 participants in the intervention group and 99 participants in the control group.

Setting

Trials were conducted in five different countries. Six trials were conducted in the United States of America (Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Robinson 2008; Rovner 2007), three trials in Denmark (Hansen 2012; Hansen 2014; Rasmussen 2003), and one trial each in Australia (Almeida 2006) and Taiwan (Tsai 2011) respectively. Narushima 2002 included participants from Argentina in addition to those from the US.

Subset data

None of the included studies used mixed study samples (e.g. a sample of participants who were initially without depression or anxiety; a sample consisting of adults who were mainly with a long-term physical condition). Two studies were of potential interest to this review (de Jonge 2009; Pols 2017) but due to mixed study samples and the unavailability of 'clear' data, we excluded them.

Participants

Psychological intervention versus control

For a comparison of psychological interventions and TAU, we analysed the data of one trial including 194 participants with age-related macular degeneration (Rovner 2007). Thirty-four percent of participants in the intervention group, and 26% in the control group were male. The average age in both groups was 81 years.

Pharmacological intervention versus placebo

For a comparison of pharmacological interventions and placebo, we analysed the data of five trials including 505 participants after stroke (Almeida 2006; Narushima 2002; Rasmussen 2003; Robinson 2008; Tsai 2011), two trials including 176 participants with head and neck cancer (Lydiatt 2008; Lydiatt 2013), one trial including 54 participants with breast cancer (Hansen 2014), one trial including 239 participants with acute coronary syndrome (Hansen 2012), and one trial including 99 participants with traumatic brain injury (Novack 2009). In the intervention groups, the average age was 60 years (range: 35 to 72 years), and about 61.8% of participants were male (range: 0% to 80%). For the control groups, the average age was 61 years (range: 35 to 68 years), and about 53% of participants were male (range: 0% to 80%). Narushima 2002 offered no information on age, and Hansen 2014 only included female participants, as they were addressing participants with breast cancer.

Interventions

Psychological intervention versus control

Rovner 2007 examined how problem-solving therapy compared to TAU might prevent the incidence of depression in participants with age-related macular degeneration. Problem-solving therapy addresses negative perceptions possibly interfering with participants practical solution skills by teaching problem-solving skills. This manual-driven interventions was administered by trained therapists (two nurses and one master's level counsellor), and delivered in six in-home problem-solving sessions (45 to 60 minutes) during a period of eight weeks. In order to maintain treatment fidelity, problem-solving sessions were audiotaped, and partially randomly assessed by one of the study authors. Ranging from 0 ('very poor') to 5 ('very good'), the study author rated 'implementing decision-making guidelines' with a mean score of 3.70 (SD = 1.30), and 'interpersonal effectiveness' with a means score of 4.97 (SD = 0.24), indicating satisfactory to very good performance. TAU consisted of usual treatments by ophthalmologists as well as other health care providers. Participants who received problem-solving therapy also received usual care.

Pharmacological intervention versus placebo

Of the ten included trials addressing pharmacological interventions to prevent depressive symptoms in adults with different long-term physical conditions, eight trials applied SSRIs (Almeida 2006; Hansen 2012; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rasmussen 2003; Robinson 2008), one trial tricyclic antidepressants (Narushima 2002), one trial an SNRI (Tsai 2011), and one trial an unclassified antidepressant (Hansen 2014).

Included SSRIs were sertraline in three trials (Almeida 2006; Novack 2009; Rasmussen 2003) with 347 participants; escitalopram in another three trials (Hansen 2012; Lydiatt 2013; Robinson 2008) with 504 participants; and citalopram (Lydiatt 2008) with 28 participants in one trial. One additional trial also administered an SSRI (fluoxetine), but given that Narushima 2002 used a three-arm parallel randomised controlled clinical design with 48 participants, we avoided the potential for bias caused by multiple comparisons with one control group by combining the two study arms, fluoxetine and nortriptyline, into one group, to create a single pair-wise comparison for meta-analysis. The duration and dosage of SSRI treatment varied greatly across studies. While all three sertraline trials administered a constant dosage of 50 mg/daily, Rasmussen 2003 allowed for a dosage increase of sertraline up to 150 mg in case of clinical need. Follow-up duration was 12 months in all three studies, but duration of treatment varied from three months (Novack 2009) to 24 weeks (Almeida 2006) to 12 months (Rasmussen 2003). As for escitalopram, dosages varied from 5 mg to 20 mg. While Hansen 2012 increased the dosage from 5 mg to 10 mg after one week until study conclusion after 12 months, Lydiatt 2013 started treatment with 10 mg, increased the dosage to 20 mg from weeks two to 16, and decreased it once more to 10 mg until the end of week 16. Robinson 2008, on the other hand, offered a constant dosage of 5 mg to those aged ≥ 65 years, and a dosage of 10 mg to those aged < 65 years during the 12 months of preventive treatment. While Hansen 2012 conducted no further follow-up after the 12 months of treatment, Robinson 2008 offered follow-up data after 18 months, and Lydiatt 2013 after 28 weeks. Considering the other two SSRIs, citalopram and fluoxetine, both administered the preventive treatment for a duration of 12 weeks.

Lydiatt 2008 started citalopram treatment with a dosage of 20 mg in the first week, continued it with 40 mg from weeks two to 11, and discontinued it after a dosage of 20 mg in week 12. Narushima 2002 steadily increased the fluoxetine dosage from 10 mg in the first three weeks, to 20 mg in weeks four to six, to 30 mg in weeks seven to nine, and finally to 40 mg in weeks 10 to 12. Follow-ups were available for citalopram after 16 weeks, and for fluoxetine after 6, 9, 12, and 24 months.

The one tricyclic antidepressant studied was nortriptyline (Narushima 2002). Corresponding to the other study arm conducted by Narushima 2002 (i.e. fluoxetine), the treatment duration with nortriptyline was three months, and follow-ups were available after six, nine, 12, and 24 months. During the treatment period, nortriptyline dosage was steadily increased from 25 mg in the first week to 50 mg in weeks two to three, to 75 mg in weeks three to six, and finally, to 100 mg in weeks 10 to 12.

The SNRI milnacipran was administered by one trial (Tsai 2011) with 92 participants. Starting the preventive treatment with a dosage of 50 mg, the dosage was increased to 100 mg after one week which participants received until the end of treatment after 12 months. No further follow-ups were available.

One trial (Hansen 2014) with 54 participants used the unclassified antidepressant melatonin in order to prevent depressive symptoms. For the duration of 13 weeks, participants scheduled for lumpectomy or mastectomy for breast cancer received a constant dosage of 6 mg melatonin, with no further follow-up data available. The first week of antidepressant treatment was administered preoperatively, the remaining 12 weeks postoperatively.

Outcomes

Seven of the 11 included trials determined incidence of depression by clinical diagnosis. Diagnoses were made by a psychiatrist according to DSM-IV (Tsai 2011), by the SCAN interview according to ICD-10 (Hansen 2012), by MINI according to DSM-IV (Lydiatt 2008), by Present State Examination (PSE) (Wing 1974) according to DSM-IV (Narushima 2002), by SCID-I according to DSM-IV (Novack 2009; Robinson 2008), or by the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott 1978; Rovner 2007). One trial assessed incidence of depression by either receiving a diagnosis of depression by a physician, or by scoring above the cut-off of a validated self-report questionnaire (Almeida 2006). The remaining three trials used cut-off scores of standardised, validated rating scales (Rasmussen 2003), or standardised, validated self-report questionnaires (Hansen 2014; Lydiatt 2013) to determine incidence of depression. The applied rating scale was the 17-item version of the HAMD, with Rasmussen 2003 using the cut-off > 18. Rasmussen 2003 also included information on the shorter 6-item version of the HAMD. However, we extracted the information of the 17-item version, as we pre-specified to select the outcome measure most frequently used across all studies, in cases where several outcome measures of the same hierarchy level were used in one study. Self-report questionnaires were HADS-D (cut-off score ≥ 8) used by Almeida 2006, the Quick Inventory of Depressive Symptomatology - Self-Rated version (QIDS-SR) (Rush 2003) (cut-off: ≥ 11) used by Lydiatt 2013, as well as the Major Depression Inventory (MDI) (Bech 2001) (cut-off: ≥ 21) used by Hansen 2014.

Adverse events were measured either by counting the total number of adverse events (Almeida 2006; Hansen 2012; Hansen 2014; Rasmussen 2003; Robinson 2008), or by counting drop-outs due to adverse events (Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Tsai 2011). Three trials, however, offered no information on adverse events (Narushima 2002; Novack 2009; Rovner 2007).

Two trials offered information on severity of depression (Novack 2009; Robinson 2008). Novack 2009 used the Neurobehavioral Functioning Inventory (NFI) Depression Subscale to determine severity of depression, and Robinson 2008 the HDRS-17.

Excluded studies

After accessing full texts, we excluded 94 trials comprising 100 full-text references from this review. We excluded 41 trials due to baseline depression. We excluded another 28 trials either because they did not include an intervention intended to target depressive symptoms, or depression was not an outcome of special interest. For example, (Beglinger 2014) used citalopram to enhance cognitive function; here, changes in depression were only secondary. Another three trials were excluded as they were not RCTs. Other reasons for exclusion were more specific. These 23 trials comprising 26 references are presented in detail in Characteristics of excluded studies.

Studies awaiting classification

Overall, we identified 13 studies still awaiting classification (see also Characteristics of studies awaiting classification). Among these, two are likely to be eligible for inclusion (ChiCTR-TRC-12003489; Sander 2017). After contacting study authors, both revealed that data collection was completed and results are in preparation for publication. Another three studies sounded promising (EudraCT-2005-005266-37; Guneri 2006; van Zyl 2006) but no corresponding published study or further data could be found. For the remaining eight studies (He 2004; Li 2004; Lu 2010; Wen 2006; Xu 2006; Zhong 2013; Zhou 2008; Zhu 2014), full texts were not accessible and no further information were available.

Ongoing studies

Two trials, both RCTs, are currently ongoing. One study examines the effects of melatonin on depression in participants with coronary syndrome (NCT02451293; Madsen 2017). The other study looks at the effects of a novel Cognitive Bias Modification intervention in the prevention of depression in participants with Alzheimer's disease (ACTRN12616000886482). See Characteristics of ongoing studies for further details.

Risk of bias in included studies

For detailed information on the risk of bias for each included study, please see the 'Risk of bias' tables in the Characteristics of included studies. A graphical representation of the overall risk of bias in included studies is presented in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3.   Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
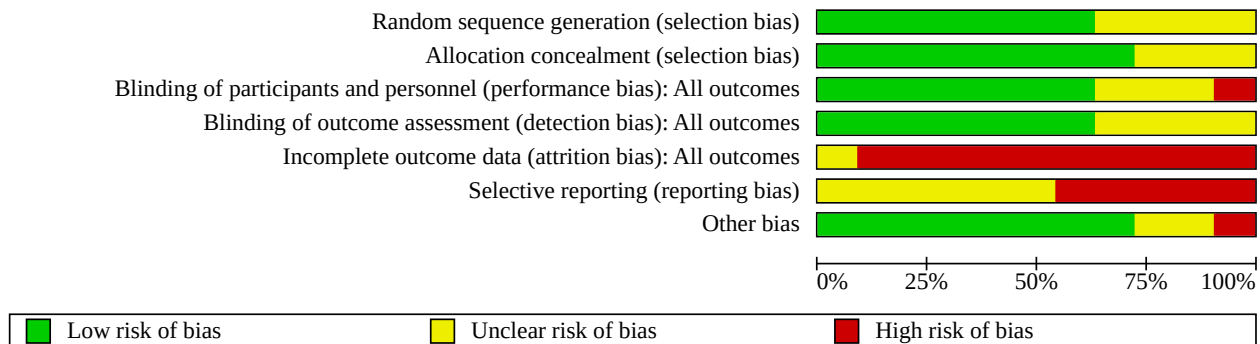
Allocation

Random sequence generation

Out of the 11 included studies, seven had low risk of bias (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Robinson 2008; Rovner 2007), and four studies an unclear risk of bias (Narushima 2002; Novack 2009; Rasmussen 2003; Tsai 2011) regarding random sequence generation.

Almeida 2006 allocated participants using a computer-generated random list of numbers. Hansen 2012 used centrally prepared randomization blocs. Hansen 2014 randomly (with a computer-generated list) assigned subjects in blocks of six. Lydiatt 2008 allocated participants by coin toss in a 1:1 fashion. Lydiatt 2013 had a pharmacist with no involvement in the evaluation assigning participants in a 1:1 ratio to either one of the conditions according to a randomization table prepared by the study statistician. Robinson 2008 used a permuted blocks randomization scheme. Therefore, the sample size was divided randomly (200 participants) into block sizes of three, six and nine and within each block participants were randomly assigned one of the three treatments using computer-generated random numbers of 1, 2, or 3. Rovner 2007 used a random-numbers table, sealed envelopes containing treatment assignments, and a fixed randomization scheme with a 1:1 allocation ratio to assign participants to one of the two study groups. To ensure balance between treatment groups Rovner 2007 applied a random block design, with block sizes (4 or 6) randomly chosen to mask the blocking process.

Narushima 2002, Novack 2009 and Rasmussen 2003 did not specify any information about randomization, and Tsai 2011 only states that they randomly assigned participants to the conditions, without more precise information.

Allocation

The risk of bias for allocation concealment was low for eight studies (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Robinson 2008; Rovner 2007; Tsai 2011). Randomisation was conducted in a decentralised manner in all of the aforementioned studies. The remaining three included studies did not specify any information about the allocation concealment (Narushima 2002; Novack 2009; Rasmussen 2003), and hence, potential bias remained unclear.

Blinding

We assessed blinding separately for performance and detection bias.

Blinding of participants and personnel (performance bias)

Seven studies (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Novack 2009; Robinson 2008; Tsai 2011) showed low risk of bias, three studies (Lydiatt 2013; Rasmussen 2003; Rovner 2007) unclear risk of bias, and one study (Narushima 2002) a high risk of bias. Studies with low risk of bias ensured unawareness of treatment allocation for both participants and study personnel (Almeida 2006; Lydiatt 2008; Hansen 2012; Hansen 2014; Novack 2009; Robinson 2008; Tsai 2011).

Even though sufficient blinding of participants and study personnel by both Lydiatt 2013 and Rasmussen 2003 can be assumed with the heading saying 'double blind', both studies received an unclear risk of bias rating as information on blinding procedures were insufficient. Rovner 2007 also received a unclear risk of bias rating even though great efforts were taken to insure study quality. Due to the nature of the intervention (problem solving therapy), participants and therapists were aware of the treatment condition. Still, research nurses instructed participants on the importance to remain silence about their study participation to avoid further bias. Despite these efforts, unmasking took place in 18% of cases.

Narushima 2002 was rated with a high risk of bias for performance bias due to the insufficient blinding of treating personnel. While efforts were made to ensure participants blinding, treating physicians appear to be aware of study conditions. In reaction to drug induced side effects in the intervention group, treatment doses were decreased for both affected participants in the intervention group and also corresponding numbers of participants in the control group. To do so, treating physicians had to be aware on both study conditions.

Blinding of outcome assessment (detection bias)

Concerning the blinding of the outcome assessment, seven studies were rated at a low risk of bias (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Narushima 2002; Novack 2009; Rovner 2007), and four studies (Lydiatt 2013; Rasmussen 2003; Robinson 2008; Tsai 2011) at an unclear risk of bias.

Almeida 2006 stated that the whole research time was blinded regarding study conditions. Hansen 2012, Hansen 2014, Lydiatt 2008, Novack 2009 and Rovner 2007 specifically mention the outcome assessment to be blinded. While Narushima 2002 offers no information on the blinding of the outcome assessors, we still rated the risk of bias being low because authors made efforts to determine the effectiveness of the blinding by asking both participants and raters if they believed they had received treatment or placebo.

All four studies (Lydiatt 2013; Rasmussen 2003; Robinson 2008; Tsai 2011) receiving an unclear bias rating and offered no information for assessing detection bias.

Incomplete outcome data

Only one of the 11 included studies (the only study offering a psychological intervention) had less than 10% of incomplete outcome data (Rovner 2007). Still, we rated the risk of attrition bias as unclear because drop-outs for the intervention group were reported incorrectly. The ten studies administering pharmacological interventions (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rasmussen 2003; Robinson 2008; Tsai 2011) were rated with a high risk of bias due to more than 10% of missing data.

Selective reporting

For six studies, there were no protocols available, so that the risk of reporting bias remained unclear (Almeida 2006; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rovner 2007). For five studies, a high risk of reporting bias was found due to incomplete reporting of outcomes (Hansen 2012; Hansen 2014; Rasmussen 2003; Robinson 2008; Tsai 2011). For only two of these trials were protocols available (Hansen 2012; Hansen 2014). The other three trials did not report completely on outcomes named in the trial registration (Robinson 2008), or in the method section (Rasmussen 2003; Tsai 2011).

Other potential sources of bias

Regarding other possible bias, eight studies showed a low risk of bias (Almeida 2006; Hansen 2012; Hansen 2014; Novack 2009; Rasmussen 2003; Robinson 2008; Rovner 2007; Tsai 2011). For two studies the risk of other bias remained unclear (Lydiatt 2008; Lydiatt 2013). One study was rated to have a high risk of other bias (Narushima 2002).

Lydiatt 2008 only offered socio-demographic data on those participants who completed visit one after four weeks, instead of those randomised and allocated, and therefore, the risk for other potential sources of bias was rated unclear. Lydiatt 2013 stratified participants by site, sex, stage, and primary modality of treatment which might also imply the potential for other sources of bias.

Narushima 2002 received a high risk of bias rating as they did not provide any information on participants' baseline characteristics (e.g. age) which hampers the evaluation of external validity. In addition, Narushima 2002 did not mention any declaration of interest, so that conflicts of interest cannot be ruled out.

Effects of interventions

See: **Summary of findings 1** Psychological interventions compared to treatment as usual in the prevention of the incidence of depression in adults with long-term physical conditions; **Summary of findings 2** Pharmacological interventions compared to placebo in the prevention of the incidence of depression in adults with long-term physical conditions

Comparison 1: Psychological interventions versus usual care

One study including 194 participants contributed data to this comparison (Rovner 2007). See also: Summary of findings 1.

Primary outcomes

1.1 Incidence of depression assessed by diagnosis: post-intervention and short-term

There was evidence of very low certainty showing that problem-solving therapy was more effective in preventing the incidence of depression than usual care immediately post-intervention (OR 0.43, 95% CI 0.20 to 0.95; participants = 194; studies = 1; Analysis 1.1). In the short-term, however, this effect was no longer meaningful (OR 0.71, 95% CI 0.36 to 1.38; participants = 190; studies = 1; Analysis 1.2).

1.2 Tolerability and acceptability of psychological interventions

The total number of adverse events, the number of drop-outs due to adverse events, and the number of drop-outs due to any cause were used as a proxy measure for tolerability and acceptability of the preventive intervention.

1.2.1 Adverse events

No data were available for this outcome.

1.2.2 Drop-outs due to adverse events

No data were available for this outcome.

1.2.3 Drop-outs due to any cause

Out of 206 participants randomised (intervention: 105; control: 101), Rovner 2007 reported on 10 participants (9.5 %) who dropped-out from the problem solving therapy study-arm, and six (2.0 %) participants who dropped out from the TAU study arm, post-intervention. Short-term, still a total of 10 participants (9.5 %) had dropped-out from the problem solving therapy study arm, and six (5.9 %) from the TAU study arm. Based on evidence of low certainty, groups differed post-intervention, with fewer drop-outs in the usual care group (OR 5.21, 95% CI 1.11 to 24.40; participants = 206; studies = 1; Analysis 1.3); but not in the short-term (OR 1.67, 95% CI 0.58 to 4.77; participants = 206; studies = 1; Analysis 1.4). For more details, see Characteristics of included studies.

Secondary outcomes

1.3 Incidence of depression assessed by cut-off

No data were available for this outcome.

1.4 Severity of depression

No data were available for this outcome.

1.5 Cost-effectiveness

No data were available for this outcome.

1.6 cost-utility

No data were available for this outcome.

Comparison 2: Pharmacological interventions versus placebo

Ten studies including 837 participants contributed data to this comparison (Almeida 2006; Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rasmussen 2003; Robinson 2008; Tsai 2011). Among these, six studies (Hansen 2012; Lydiatt 2008; Narushima 2002; Novack 2009; Robinson 2008; Tsai 2011) reported on the incidence of depression assessed by diagnosis, our primary outcome. Three studies (Hansen 2014; Lydiatt 2013; Rasmussen 2003) assessed incidence of depression by scoring above a certain cut-off score (i.e. secondary outcome), and one study (Almeida 2006) assessed incidence of depression either by diagnosis of a treating physician, or by scoring above a certain cut-off. For the post-intervention effect, Analysis 2.1 offers an overview on the incidence of depression irrespective of the pre-defined primary and secondary outcomes. (Only nine studies are presented for the post-intervention effect because one study (Lydiatt 2008) only offered data on the short-term effect (see Primary outcomes)). Hence, there was evidence of very low certainty showing that pharmacological interventions (escitalopram, fluoxetine/nortriptyline, melatonin, milnacipran, sertraline) were more effective than placebo in preventing the incidence of depression, assessed either by diagnosis or cut-off, immediately post-intervention (OR 0.31, 95% CI 0.20 to 0.49; 814 participants; nine studies; $I^2 = 0\%$). In the medium-term, differences between pharmacological interventions (escitalopram, sertraline) and placebo were no longer meaningful (OR 0.81, 95% CI 0.23 to 2.82; 233 participants; three studies; $I^2 = 49\%$; Analysis 2.2). The considerable heterogeneity is most likely attributable to the one study favouring the placebo group instead of the pharmacological group.

The following sections report results in accordance to the prespecified classifications of primary or secondary outcomes.

For overall results, see also: Summary of findings 2.

Primary outcomes

2.1 Incidence of depression assessed by diagnosis: post-intervention, short-term, and medium-term

Assessed by diagnosis, there was evidence of very low certainty showing that pharmacological interventions (escitalopram, fluoxetine/nortriptyline, milnacipran, sertraline) were more effective than placebo in preventing the incidence of depression immediately post-intervention (OR 0.26, 95% CI 0.13 to 0.52; participants = 474; studies = 5; $I^2 = 0\%$: Analysis 2.3). Very low-certainty evidence on the short-term effect (OR 0.44, 95% CI 0.08 to 2.46; participants = 23; studies = 1; Analysis 2.4), or the medium-term effect (OR 1.50, 95% CI 0.06 to 39.71; participants = 139; studies = 2; $I^2 = 75\%$; Analysis 2.5) yielded no meaningful group differences (short term: only citalopram; medium-term: escitalopram, sertraline).

2.2 Tolerability and acceptability for pharmacological interventions

2.2.1 Adverse events

Five studies reported adverse events in detail (Almeida 2006; Hansen 2012; Hansen 2014; Rasmussen 2003; Robinson 2008). In total, 669 adverse events were reported from 316 participants in the pharmacological group, and 610 adverse events from 311 participants in the placebo group (escitalopram: n = 459 versus

placebo: n = 389; melatonin: n = 29 versus placebo: n = 15; sertraline: n = 181 versus placebo: n = 206).

Almeida 2006 found 46 adverse events in participants after stroke, treated with sertraline, and 25 events in those treated with placebo. According to Fisher's exact test, group differences existed for tremor (P = .005), and agitation (P = .026), with less tremor (23.3% vs. 0.0%) and less agitation (23.3% vs. 3.2%) in the placebo group.

Also treated with sertraline, and measured by the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, Rasmussen 2003 reported no meaningful group differences for the incidence of adverse events in participants after stroke. In total, the intervention group experienced about 170 adverse events, and the control group about 200 adverse events including tiredness: 44% (sertraline) and 50% (placebo) respectively; restlessness/tension: 37% and 49%; depressed mood: 36% and 47%; dizziness: 23% and 24%; poor concentration: 20% and 32%; insomnia: 16% and 25%; constipation: 11% and 16%; diarrhoea: 16% and 11%; nausea: 16% and 11%; increased sleep: 11% and 10%; headache: 9% and 10%; and poor memory: 4% and 13%.

Robinson 2008 assessed a variety of adverse events in participants after stroke treated with escitalopram. In the escitalopram group, 2 to 29% of participants experienced some kind of gastrointestinal adverse events (total number: 73 gastrointestinal adverse events), 7 to 20% some kind of sexual adverse events (total number: 22 sexual adverse events), 8 to 64% some kind of cardiovascular adverse events (total number: 51 cardiovascular adverse events), and 2 to 63% some other kind of adverse event like dizziness (total number: 74 other adverse events). Including all-cause hospitalizations, nausea, and adverse effects associated with escitalopram were not significantly different between the study groups. In the placebo group, 2 to 47% of participants after stroke experienced some kind of gastrointestinal adverse events (total number: 81 gastrointestinal adverse events), 2 to 16% some kind of sexual adverse events (total number: 14 sexual adverse events), 5 to 62% some kind of cardiovascular adverse events (total number: 46 cardiovascular adverse events), and 2 to 59% some other kind of adverse event like dizziness (total number: 61 other adverse events). While no test statistics were reported, Robinson 2008 state that there were no significant differences between groups. In total, the escitalopram group experienced 220 adverse events, and the placebo group 202 adverse events.

Hansen 2012 assessed the effects of escitalopram on participants with acute coronary syndrome. Also using the UKU side effect scale, authors state there were no differences between groups except for increased dream activity. In total, the escitalopram group experienced about 239 adverse events, and the placebo group about 187, including gastrointestinal adverse effects (23 vs. 16), sexual adverse effects (42 vs. 30), or other adverse effects (174 vs. 141)

For participants with breast cancer, Hansen 2014 report no significant group differences between the melatonin group (15/27 = 56%) and the placebo group (12/24 = 50%) regarding adverse events (P = 0.78). In the melatonin group, most frequent adverse events were dizziness (14%), headache, (10%) and paraesthesia in the mouth region, arms or legs (10%). In the placebo group, the most common adverse events were headache (27%), difficulty falling asleep (13%), and nausea (13%). The total numbers of adverse events were 29 in the melatonin group, and 15 in the placebo group.

2.2.2 Drop-outs due to adverse events

Five studies reported data on drop-outs associated with the incidence of adverse events Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Tsai 2011 (for details see Characteristics of included studies). There was evidence of very low certainty showing that a placebo intervention resulted in fewer drop-outs due to adverse events than a pharmacological intervention (OR 2.05, 95% CI 1.07 to 3.89; participants = 561; studies = 5; I² = 0%; Analysis 2.6).

2.2.3 Drop-outs due to any cause

Nine studies included data on drop-outs due to any cause directly post-intervention (Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Narushima 2002; Novack 2009; Rasmussen 2003; Robinson 2008; Tsai 2011). There was evidence of very low certainty showing no group difference between pharmacological interventions and placebo regarding drop-outs due to any cause (OR 1.13, 95% CI 0.73 to 1.73; participants = 962; studies = 9; I² = 28%; Analysis 2.7). Rasmussen 2003 reported a total drop-out of 12.9% (9/70) in the sertraline group, and 14.9% (10/67) in the placebo group for participants after stroke. Novack 2009 reported a total drop-out of 0.5% (1/49) in the sertraline group, and 4.0% (2/50) in the placebo group for participants with traumatic brain injury. Robinson 2008 reported a total drop-out of 11.9% (7/59) in the escitalopram group, and 8.6% (5/58) in the placebo group for participants after stroke. Lydiatt 2013 reported a total drop-out of 51.4% (38/74) in the escitalopram group, and 40.5% (30/74) in the placebo group for participants with head and neck cancer. Hansen 2012 reported a total drop-out of 29.2% (35/120) in the escitalopram group, and 25.2% (30/119) in the placebo group for participants with acute coronary syndrome. One additional participant of the placebo group was excluded due to protocol violation. Hansen 2014 reported a significant difference between groups (P = .002), with a total drop-out of 3.6% (1/28) in the melatonin group, and 38.5% (10/26) in the placebo group for participants with breast cancer. Lydiatt 2008 reported a total drop-out of 13.3% (2/15) in the citalopram group, and 23.1% (3/13) in the placebo group for participants with head and neck cancer. Narushima 2002 reported a total drop-out of 12.5% (4/32) in the fluoxetine/nortriptyline group, and 6.3% (1/16) in the placebo group for participants after stroke. Tsai 2011 reported no significant differences between groups (P = .20), with a total drop-out of 45.7% (21/46) in the milnacipran group, and 32.6% (15/46) in the placebo group for participants after stroke.

Three studies included data on drop-outs due to any cause medium-term (Almeida 2006; Novack 2009; Robinson 2008). There was evidence of very low certainty showing no group difference between pharmacological interventions and placebo regarding drop-outs due to any cause (OR 1.13, 95% CI 0.69 to 1.86; participants = 327; studies = 3; I² = 0%; Analysis 2.8). Almeida 2006 reported a total drop-out of 20.0% (11/55) in the sertraline group, and 10.7% (6/56) in the placebo group for participants after stroke. Novack 2009 reported a total drop-out of 26.5% (13/49) in the sertraline group, and 28.0% (14/50) in the placebo group for participants with traumatic brain injury. Robinson 2008 reported a total drop-out of 42.4% (25/59) in the escitalopram group, and 43.1% (25/58) in the placebo group for participants after stroke.

For more detailed information on drop-outs due to any cause see Characteristics of included studies.

Secondary outcomes

2.3 Incidence of depression assessed by cut-off

There was evidence of very low certainty on pharmacological interventions (escitalopram, melatonin, sertraline) being more effective than placebo in preventing the incidence of depression immediately post-intervention (OR 0.26, 95% CI 0.13 to 0.53; participants = 228; studies = 3; I² = 0%; Analysis 2.9

2.4 Incidence of depression assessed by either diagnosis or cut-off

One trial of very low certainty assessed incidence of depression by either diagnosis or cut-off. The pharmacological intervention sertraline showed no meaningful group differences post-intervention (OR 0.73, 95% CI 0.26 to 2.00; participants = 99; studies = 1; Analysis 2.10), or medium-term (OR 0.69, 95% CI 0.27 to 1.74; participants = 94; studies = 1: Analysis 2.11).

2.5 Severity of depression

Evidence addressing severity of depression was of very low certainty. Comparing pharmacological interventions (sertraline, escitalopram) to placebo yielded no meaningful differences regarding severity of depression, neither post-intervention (SMD -0.19, 95% CI -0.91 to 0.54; participants = 163; studies = 2; I² = 81%; Analysis 2.12), nor short-term (SMD -0.33, 95% CI -0.75 to 0.09; participants = 87; studies = 1; Analysis 2.13), nor in the medium-term (SMD 0.18, 95% CI -0.72 to 1.09; 139 participants; two studies; I² = 86%; Analysis 2.14). Note that heterogeneity was considerable for the post-intervention and medium-term effect, which is most likely attributable to the different types of depression scales used (HDRS-17 and NFI).

2.6 Cost-effectiveness

No data were available for this outcome.

2.7 Cost-utility

No data were available for this outcome.

Subgroup analyses

Subgroup analyses were planned for the type of long-term physical condition, type of psychological intervention, as well as the class of antidepressant. To compare at least two types either of long-term physical conditions, two types of psychological interventions, or two classes of antidepressants, three or more studies had to be available for each particular group.

3.1 Type of long-term physical condition

Due to a lack of more studies on the same type of disease (except for stroke), no subgroup analyses were conducted for a comparison between acute coronary syndrome, age-related macular degeneration, breast cancer, head and neck cancer, stroke or traumatic brain injury.

3.2 Type of psychological intervention

Only one study (Rovner 2007) addressed a psychological intervention (problem solving therapy), and hence, no additional subgroup analyses were conducted.

3.3 Class of antidepressant

Across studies, different classes of antidepressant medication were applied to prevent the onset of depressive symptoms. Due to a lack of studies on other classes of antidepressant medications like SSRIs (e.g. escitalopram and sertraline), SNRIs (e.g. milnacipran), tricyclic antidepressant medication (e.g. nortriptyline), and unclassified antidepressant (e.g. melatonin) we were unable to conduct subgroup analyses by class of antidepressant.

Sensitivity analyses

4.1 Assessment method

4.1.1 Comparison 1: Psychological interventions versus usual care

Not applicable. Only one study was included for this outcome.

4.1.2 Comparison 2: Pharmacological interventions versus placebo

Not applicable. Studies using cut-offs to assess incidence of depression (Hansen 2014; Lydiatt 2013; Rasmussen 2003) used different types of instruments (MDI: Hansen 2014; QIDS-SR: Lydiatt 2013; HAM-D 17-item version: Rasmussen 2003).

4.2 Quality of studies

4.2.1 Comparison 1: Psychological interventions versus usual care

4.2.1.1 Failing to double-blind

Not applicable.

4.2.1.2 Lacking proper allocation concealment

Not applicable.

4.2.1.3 Impact of missing data

We conducted best-case analyses where all drop-outs in the control group were considered to have an occurrence of depression. In the best-case scenario, problem-solving therapy was more effective in the prevention of the incidence of depression than usual care, both immediately post-intervention (OR 0.36, 95% CI 0.16 to 0.77; 206 participants; one study), and in the short-term (OR 0.51, 95% CI 0.27 to 0.96; 206 participants; one study; Analysis 3.1). Compared to original analyses, in a best-case scenario the short-term effect was beneficial as well.

We also conducted worst-case analyses where all drop-outs in the intervention group were considered to have an occurrence of depression. In the worst-case scenario, effects were no longer favouring either group, neither immediately post-intervention (OR 0.85, 95% CI 0.44 to 1.65; 206 participants; one study), nor in the short-term (OR 1.15, 95% CI 0.62 to 2.13; 206 participants; one study; Analysis 3.2). Assuming a worst-case scenario, the post-intervention effect was no longer beneficial with respect to the intervention group.

4.2.1.4 Cluster-randomised trials

Not applicable.

4.2.2 Comparison 2: Pharmacological interventions vs. placebo

4.2.2.1 Failing to double-blind

Only one study posed a high risk of bias by lacking proper blinding (Narushima 2002). Therefore, we conducted a sensitivity analysis excluding this study in order to assess the incidence of depression after preventive pharmacological treatment. Hence, even after exclusion of Narushima 2002 there was evidence that pharmacological interventions (escitalopram, milnacipran, sertraline) were more effective than placebo in preventing the incidence of depression assessed by diagnosis immediately post-intervention (OR 0.24, 95% CI 0.11 to 0.53; 431 participants; four studies; $I^2 = 0\%$; Analysis 4.1). Overall, the tendency of the effect did not change after excluding Narushima 2002.

4.2.2.2 Lacking proper allocation concealment

Not applicable.

4.2.2.3 Impact of missing data

We conducted best-case analyses where all drop-outs in the placebo group were considered to have an occurrence of depression. Overall interpretation of results did not change after conducting best case analyses. Again, we found group differences favouring the intervention group immediately post-intervention (OR 0.13, 95% CI 0.07 to 0.24; 1045 participants; nine studies; $I^2 = 50\%$), and no group differences in the short term (OR 0.31, 95% CI 0.06 to 1.51; 28 participants; one study), and the medium term (OR 0.16, 95% CI 0.06 to 0.43; 327 participants; three studies; $I^2 = 59\%$; Analysis 5.1).

We also conducted worst-case analyses where all drop-outs in the intervention group were considered to have an occurrence of depression. Immediately post-intervention (OR 1.35, 95% CI 0.74 to 2.44; 1045 participants; nine studies; $I^2 = 69\%$) as well as in the short-term (OR 1.07, 95% CI 0.23 to 4.89; 28 participants; one study; $I^2 = 0\%$), worst-case scenarios yielded no meaningful group differences (Analysis 5.2). Compared to the original analyses, the worst-case scenario no longer found a beneficial post-intervention effect for the intervention group post-intervention. In the medium term, worst-case analyses showed a meaningful effect favouring the placebo group (OR 4.81, 95% CI 0.92 to 25.29; 327 participants; three studies; $I^2 = 81\%$). Original results favoured neither group but worst-case analyses indicated a beneficial effect for the placebo group.

4.2.2.4 Cluster-randomised trials

Not applicable.

4.3 Selection of patients

4.3.1 Comparison 1: Psychological interventions vs. usual care

No data were available for this outcome.

4.3.2 Comparison 2: Pharmacological interventions vs. placebo

No data were available for this outcome.

4.4 Lengths of treatment

To evaluate the sustainability of possible antidepressant effects we conducted analyses where follow-up was post-randomisation instead of post-intervention.

4.4.1 Comparison 1: Psychological interventions vs. usual care

Only one study addressing problem solving therapy was included (Rovner 2007). Therefore, effects were the same as post-

intervention but time frames for the considered length of treatment changed. If follow-up was post-randomisation instead of post-intervention, the post-intervention effect would be a short-term effect (Analysis 1.1), and the short-term effect a medium-term effect (Analysis 1.2).

4.4.2 Comparison 2: Pharmacological interventions vs. placebo

For the primary outcome, we derived short-term effects from six studies (assessed by diagnosis: Lydiatt 2008, Narushima 2002, Novack 2009; assessed by cut-off: Hansen 2014, Lydiatt 2013; assessed by either diagnosis or cut-off: Almeida 2006), a medium-term effect from six studies (assessed by diagnosis: Hansen 2012, Novack 2009, Robinson 2008, Tsai 2011; assessed by cut-off: Rasmussen 2003; assessed by either diagnosis or cut-off: Almeida 2006), and a long-term effect from one study (assessed by diagnosis: Robinson 2008). There was evidence that pharmacological interventions were more effective than placebo in preventing the incidence of depression in the short-term (OR 0.36, 95% CI 0.21 to 0.64; 384 participants; six studies; I^2 = 2%; Analysis 6.1). In the medium term, there was also a meaningful effect favouring pharmacological interventions to placebo in the prevention of the incidence of depression (OR 0.37, 95% CI 0.22 to 0.61; 619 participants; six studies; I^2 = 0%; Analysis 6.2). In the long term, groups were not different from one another (OR 9.89, 95% CI 0.51 to 191.27; 67 participants; one study; Analysis 6.3).

4.5 Type of funding

To evaluate potential bias towards funders' interests, we excluded studies based on commercial funding.

4.5.1 Comparison 1: Psychological interventions versus usual care

Not applicable.

4.5.2 Comparison 2: Pharmacological interventions versus placebo

We excluded Rasmussen 2003 as they received funding by Pfizer A/S. Robinson 2008 received no funding from pharmaceutical companies but authors were involved with e.g. Hamilton Pharmaceutical Company, Avanir Pharmaceutical Company, Forest Laboratories, or Pfizer. Even though authors stated that Hamilton Pharmaceutical Company and Avanir Pharmaceutical Company had no financial interest in their prevention study, we excluded Robinson 2008 as well.

Even after the exclusion of Rasmussen 2003 and Robinson 2008, there was evidence that pharmacological interventions (escitalopram, fluoxetine/nortriptyline, melatonin, milnacipran, sertraline) were still more effective than placebo in preventing the incidence of depression assessed by either diagnosis or cut-off immediately post-intervention (OR 0.31, 95% CI 0.18 to 0.54; 591 participants; seven studies; I^2 = 2%; Analysis 7.1). As before, in the medium term group differences between pharmacological interventions (escitalopram, sertraline) and placebo were no longer meaningful (OR 0.58, 95% CI 0.26 to 1.26; 166 participants; two studies; I^2 = 0%; Analysis 7.2).

Reporting bias

We intended to minimise the impact of reporting bias by conducting an extensive and sensitive systematic search for literature.

5.1 Comparison 1: Psychological interventions vs. usual care

Not applicable, there were insufficient studies to assess reporting bias.

5.2 Comparison 2: Pharmacological interventions vs. placebo

The funnel plot for the primary outcome pharmacological intervention showed evidence of asymmetry (see Figure 4), and therefore, a risk of reporting bias has to be assumed.

DISCUSSION

Our review gives a comprehensive overview of primary preventive interventions to prevent depression in adults with long-term physical conditions, irrespective of the type of intervention or the type of long-term physical condition. Therefore, we included both psychological and pharmacological interventions applied in primary prevention trials. Primary prevention trials are characterised by starting a treatment before any relevant symptoms develop; in our case, symptoms of depression. Due to the fact that a majority of antidepressant treatments are associated with a variety of adverse events and increased healthcare costs, the initiation of antidepressant treatment before the onset of any clinical relevant symptoms needs to be highly justified. Hence, the WHO encourages applying certain prevention programs and treatments only to a selected group of people known to be at high risk for a disease; such as, for example, depression (selective prevention) (WHO 2016). People with long-term physical conditions are considered to be at high risk for developing depressive symptoms, and hence, are considered to be a appropriate group for prevention trials (WHO 2016). However, the types of long-term physical conditions are not specified, even though some types like coronary heart disease, stroke, cancer, or diabetes are suggested (WHO 2016). Therefore, we included all types of long-term physical conditions in order to also identify those potentially receptive to prevention approaches. To do so, we developed an extensive search strategy in close collaboration with the Cochrane Common Mental Disorder Group, which intended to incorporate at once all types of long-term physical conditions according to ICD-10 criteria. With the magnitude of different types of long-term physical conditions as well as the specialised expertise required to deal with them, it is very hard for clinicians and researchers alike to have an overview on current developments. By including all types of diseases and applying a sensitive search scheme, we also hoped to identify types of long-term physical conditions that might show a potential for primary prevention treatments. When conducting this review, we did not expect any concluding realisations in this broad field. However, we wanted to summarise international prevention trials on certain diseases already deemed potentially receptive to primary prevention by experts around the world. We hope that our findings can aid future research to broach certain types of long-term physical conditions when considering future primary prevention trials.

Summary of main results

Regarding **psychological interventions**, there was evidence of very low certainty for a beneficial post-intervention effect of problem-solving therapy compared to TAU in preventing the incidence of depression in adults with age-related macular degeneration. However, no group differences could be found at six to 12 months follow-up. For our other primary outcomes, tolerability and acceptability for psychological interventions, there

were no data available on adverse events, or drop-outs due to adverse events. As for drop-outs due to any cause, there was evidence of low certainty showing fewer drop-outs in the usual care group directly post-intervention. in the short term, however, the two groups no longer differed.

There were no data on our secondary outcomes (severity of depression, cost-effectiveness, or cost-utility). See also Summary of findings 1.

For psychological interventions, we undertook sensitivity analyses on the 'quality of studies - impact of missing data,' as well as the 'length of treatment.'

To assess the 'impact of missing data', we conducted best-case analyses where all drop-outs in the control group were considered to have an occurrence of depression, and worst-case analyses where all drop-outs in the intervention group were considered to have an occurrence of depression. In the best-case scenario, in addition to the beneficial post-intervention effect, problem-solving therapy appeared to be also beneficial in the short-term. In the worst case scenario, post-intervention effects initially favouring the intervention group were no longer favouring either group. In the short term, there was no difference between original analyses and the worst-case scenario, and no meaningful group differences in either scenario.

In order to analyse the sustainability of possible antidepressant effects after the preventive intervention has been finished, we conducted the primary outcome analyses where follow-up was post-intervention. This approach might mix preventive interventions with very short and very long intervention periods (e.g. combining ultra brief prevention measures of only a few sessions within days compared to an e.g. 12 months prevention measure). In both cases, we would examine the maintenance effects of these interventions, while we would obviously expect a stronger maintenance effect from a prevention intervention lasting 12 months. However, to gain information on the prevention effect of an intervention in a given time period, e.g. 12 months following recruitment/intervention start, we conducted sensitivity analyses where follow-up was post-randomisation instead of post-intervention. In this case, we mixed interventions that already ended (e.g. a short-term intervention) and already looked at sustainability effects with interventions that are at its post-treatment effect after 12 months. For psychological interventions, results remained unchanged. If follow-up was post-randomisation instead of post-intervention, the post-intervention effect would be a less than six months post-randomisation effect, and the short-term effect a six to 12 months post-randomisation effect.

Regarding **pharmacological interventions**, there was evidence of only very low certainty for a beneficial post-intervention effect of antidepressants (escitalopram, fluoxetine/nortriptyline, melatonin, milnacipran, or sertraline) compared to placebo in preventing the incidence of depression in adults with acute coronary syndrome, breast cancer, head and neck cancer, stroke or traumatic brain injury. One trial including the antidepressant citalopram did not provide post-intervention data but data for the 0 to 6 months follow-up. Here, a comparison of citalopram to placebo for adults with head and neck cancer yielded no meaningful group differences. Assessing the effects for the 6 to 12 months follow-up revealed no group differences for sertraline in the preventive treatment of adults with stroke or traumatic brain

injury either. For our other primary outcome - tolerability and acceptability of pharmacological interventions - only some of the studies reported on these outcomes. As for adverse events, the total number was somewhat comparable between the pharmacological intervention (n = 669) and the placebo group (n = 610). Analysing drop-outs due to adverse events, data synthesis of five studies revealed less drop-outs due to adverse events in the placebo group. Concerning drop-outs due to any cause, no group differences could be found. With respect to our secondary outcomes, only two studies reported on severity of depression, and no data at all was available for cost-effectiveness, or cost-utility. Regarding severity of depression, evidence of very low certainty showed no group differences comparing pharmacological interventions (sertraline, escitalopram) to placebo post-intervention, 0 to 6 months follow-up, or six to 12 months follow-up. For an overview of our major findings, see also Summary of findings 2.

Due to lack of data, we were unable to conduct subgroup analyses on types of long-term physical conditions, types of psychological interventions, or classes of antidepressants.

Our sensitivity analyses on the quality of 'studies - failing to double blind' as well as the 'type of funding' revealed no changes in the overall interpretation of results.

When conducting sensitivity analyses on the 'quality of studies - impact of missing data' for pharmacological interventions, our overall interpretation of results did not change after conducting best-case analyses. Worst-case analyses annihilated the beneficial post-intervention effect. At less than six months follow-up there were no differences. However, at six to 12 months follow-up, the worst-case scenario revealed a meaningful effect favouring the placebo group instead of antidepressant treatments.

Regarding the 'length of treatment', conducted sensitivity analyses revealed that less than six months post-randomisation pharmacological interventions (citalopram, escitalopram, fluoxetine/nortriptyline, melatonin, sertraline) were more effective than placebo. Six to 12 months post-randomisation, there was also a meaningful effect favouring pharmacological interventions (escitalopram, milnacipran, sertraline) to placebo in the prevention of the incidence of depression. Only In the long-term (more than 12 months follow-up), groups were not different from one another.

Overall completeness and applicability of evidence

In total, we included six different types of long-term physical conditions (acute coronary syndrome, age-related macular degeneration, breast cancer, head and neck cancer, stroke, and traumatic brain injury) and eight types of treatments. The psychological intervention was problem solving therapy, and the seven types of pharmacological interventions included citalopram, escitalopram, fluoxetine/nortriptyline, melatonin, milnacipran, and sertraline. Stroke was the only condition addressed more extensively with five included trials. Most common pharmacological treatments were SSRIs with three trials including escitalopram and sertraline respectively, as well as one trial including citalopram.

Our analyses were conducted following the 'per protocol' principle. Especially with regard to pharmacological antidepressant agents, we assumed that adverse events might arise due to the treatment

itself or the development of depressive symptoms, and therefore, might pose the major reasons for discontinuation of study participation. Of the included trials, six conducted ITT analyses (Hansen 2012; Hansen 2014; Lydiatt 2013; Novack 2009; Robinson 2008; Tsai 2011), and five conduced PP analyses (Almeida 2006; Lydiatt 2008; Narushima 2002; Rasmussen 2003; Rovner 2007). In order to report incidences of depression following the PP principle, we re-calculated the total N of the ITT trials, i.e. we took the total number of randomised participants (e.g. N = 100) and subtracted the total number of drop-outs (e.g. N = 5) for each corresponding follow-up (e.g. 100 minus 15 = 85). An exemplary incidence of 20 would be 20/85 (i.e. PP) instead of 20/100 (ITT). To account for the missing data due to drop-outs as well, we conducted sensitivity analyses on best case and worst case scenarios.

The interpretation of results derived for psychological interventions aimed at the prevention of depression is limited. Even though relatively well conducted, only one trial (Rovner 2007) dealt with the beneficial effects of psychological preventive interventions. Next to the general reporting of drop-outs, no information on our second primary outcome 'acceptability and tolerability' were reported. In addition, no information on our secondary outcomes severity of depression, cost-effectiveness, or cost-utility were available. One trial (Robinson 2008) included a third study arm on a psychological intervention which was not reported due to the fact that an appropriate control group was missing. Therefore, only the comparison of escitalopram and placebo was included in our review, even though results indicate an even greater beneficial effect of problem solving therapy than escitalopram in adults after stroke. Also due to unsuitable control groups, two studies were not included in our review (Niedermaier 2004; Zhang 2013). Both trials included pharmacological interventions which were compared to treatment as usual. With our focus on psychotherapeutic psychological interventions, we did not explore the wide range of preventative social or lifestyle interventions that might also prove to be beneficial in the prevention of depression (Natale 2019).

The interpretation of results derived for pharmacological interventions aimed at the prevention of depression is limited as well. Only six of the ten included trials offered information on our primary outcome 'incidence of depression' assessed by diagnosis (Hansen 2012; Lydiatt 2008; Narushima 2002; Novack 2009; Robinson 2008; Tsai 2011). To enhance the visibility of results regarding the incidence of depression, we decided to include both the primary (i.e. diagnosis) and the secondary (i.e. cut-off) outcome in one forest plot. Three trials (Hansen 2014; Lydiatt 2013 Rasmussen 2003) assessed the incidence of depression only by scoring above a certain cut-off (i.e. secondary outcome), and one trial (Almeida 2006) used the mixed method of assessing the incidence of depression by either diagnosis by a physician, or cut-off. This made it possible to compute an overall effect for the incidence of depression as well as subgroup results for either diagnosis (i.e. high quality of assessment), or cut-off (i.e. low quality of assessment). Unfortunately, one trial (Lydiatt 2008) offered no information on the post-intervention effect but only on the short-term effect. Our major analyses (Analysis 3.1, Figure 8) on the preventive effects of pharmacological interventions therefore only includes the data of nine trials. Interpretation of data was further complicated by imprecise reporting. One trial (Rasmussen 2003) only reported percentages instead of total numbers, so we had to calculate the latter. Two trials (Novack 2009; Rasmussen

2003) presented inconclusive numbers on drop-outs. After re-calculation of e.g. percentages, we chose the data adding up best. One study (Narushima 2002) had a mixed study-arm regarding the intervention. Here, participants received either fluoxetine, a SSRI, or nortriptyline, a tricyclic antidepressant. Given that both antidepressants origin from a different antidepressant class makes interpretation of the data even harder. Even though Narushima 2002 included 3, 6, 9, 12, and 24 months follow-ups, we could not extract the corresponding data except for the 3 months follow-up. For the latter, data was presented in the text. For the other follow-ups, only a graphical presentation of the outcome data was a available. The kind of graphical representation, however, made it impossible for us to do reasonable data extractions. As for our second primary outcome, only five out of ten trials reported information on drop-outs due to adverse events (Hansen 2012; Hansen 2014; Lydiatt 2008; Lydiatt 2013; Tsai 2011), and five studies report on adverse events in total (Almeida 2006; Hansen 2012; Hansen 2014; Rasmussen 2003; Robinson 2008). While this offers first hints of the acceptability and tolerability of the study medication, more detailed information are necessary to allow for a recommendation of safe administration of preventive antidepressant medication in adults with long-term physical conditions. As of right now, it appears that the study medication caused more drop-outs due to adverse events than the placebo medication, and hence, should implicitly be considered when interpreting these results.

Regarding the remaining secondary outcomes, no conclusions can be drawn. Using different instruments, only two of the included studies (Novack 2009; Robinson 2008) addressed severity of depression for adults after stroke or with traumatic brain injury. Cost-effectiveness and cost-utility were not assessed at all. The latter is a common shortcoming in these kind of studies.

Studies were excluded mostly due to an inconsistent understanding of prevention. A lot of studies included complete samples or subsamples of adults who were already depressed. In these cases, major study aims mainly were the decline in disease progression, or the treatment of subthreshold depression (i.e. secondary prevention) (see also Characteristics of excluded studies). Future research might benefit from a more specific definition of the kind of prevention in accordance with e.g. classifications made by the WHO (e.g. WHO 2016).

Surprisingly, one trial could not be included as it did not report any incidence of depression, even though it aspired to examine the preventive effects of fluoxetine in adults after stroke (Kong 2007).

In summary, generalisation of results and corresponding conclusions cannot be drawn. Regarding the type of long-term physical condition, adults after stroke pose the only subgroup that might allow for any conclusions on the preventive effects of pharmacological interventions for the incidence of depression. However, types of treatments varied greatly, with two trials applying sertraline, one trial fluoxetine/nortriptyline, one trial escitalopram, and one trial milnacipran. Among these, three trials assessed incidence by diagnosis, one trial by cut-off, and one trial by either diagnosis or cut-off. Heterogeneity regarding sample size was great as well, and hence, no generalisable conclusions can be drawn for adults after stroke.

Quality of the evidence

Using the risk of bias assessments for each study as well as GRADEpro GDT to rate the certainty of the evidence, we find there are serious shortcomings regarding the certainty of the evidence. Overall, the certainty of the evidence was rated very low to low. We were unable to identify any studies free of risk of bias. One of the major concerns of this review was the lack of complete outcome data, and inadequate reporting of adverse events and reasons for drop-out. We assume that adverse events might arise due to the treatment or the development of depressive symptoms, and therefore, might pose the major reasons for discontinuation of study participation. Incomplete or inadequate reporting of this very central outcome caused us to assume a strong risk of bias. Also, all studies were rated at high or unclear risk of bias regarding selective reporting. For only two of the included trials (Hansen 2012; Hansen 2014) could we identify a corresponding protocol. The trial conducted by Rovner 2007 on the preventive effect of a psychological intervention was at the least risk of bias. Overall, inconsistency was rated mostly 'not serious' with minor exceptions regarding the medium-term effect of pharmacological interventions. Due to the nature of this review (several types of long-term physical conditions as well as different types of pharmacological treatments and applied dosages), we had to downgrade the certainty of the evidence once. Regarding the primary outcomes, imprecision was not serious for the psychological prevention trial but very serious for pharmacological interventions (downgraded twice). The latter showed small sample sizes, only few events, and/or wide confidence intervals.

Potential biases in the review process

By predefining the methodological procedures and the selection of outcomes and analyses in the protocol, by involving the Cochrane Mental Disorders Group when defining both the definitions of 'primary prevention' and 'selective prevention' as well as the list of diseases considered to be 'long-term physical conditions', and by assigning two independent review authors to the task of study selection, we do not consider the review process to be likely to be biased. Still, it is limited be the small number of identified relevant studies. In addition, we might not have identified all grey literature and unpublished studies, and therefore, missing grey literature and unpublished RCTs might have led to an overestimation of prevention effects (McAuley 2000).

Agreements and disagreements with other studies or reviews

A variety of Cochrane Reviews have been undertaken to address depression in long-term physical conditions. There is evidence for beneficial effects of antidepressant interventions for depressed adults with cancer (Ostuzzi 2018), coronary artery disease (Baumeister 2011b), coronary heart disease (Richards 2017), diabetes mellitus (Baumeister 2012c), and stroke (Hackett 2008b). These data imply the potential of treatment approaches in several long-term physical conditions, and might guide decision making when choosing the types of interventions that could also serve as preventive interventions for certain types of long-term physical conditions. For example, there is also evidence for beneficial effects of pharmacological preventive interventions (including secondary prevention approaches) on depression in adults after stroke (Hackett 2008a). This corresponds with our results but it must be noted that some of the included studies are the same as in our review. The potential of preventive psychological interventions for patients after stroke is yet unknown. As for primary prevention, we could not identify any studies including psychological interventions. However, Hackett 2008a found no beneficial effects for psychological interventions in the general prevention of depression in adults after stroke, and therefore, it might be less likely that psychological interventions might be useful as a primary prevention in adults after stroke. For other long-term physical conditions such as diabetes (Baumeister 2012c), or coronary heart and artery diseases (Baumeister 2011b; Richards 2017), psychological interventions were effective in treating depression and might be considered as primary preventive interventions in these diseases as well. At present, we could identify no RCTs addressing primary preventive psychological interventions in these diseases.

AUTHORS' CONCLUSIONS

Implications for practice

With only 11 trials of low- to very-low certainty of evidence included in this review, there is only uncertain evidence regarding the implementation of primary prevention treatments. The available evidence included six different types of long-term physical conditions, but also different types of treatments (problem-solving therapy as well as seven types of antidepressant medications). Adults after stroke were the group of people addressed most often (five trials) but results remain heterogeneous, as participants received five different types of antidepressant medication of different dosages. Heterogeneity across trials was substantial and limited the interpretation and certainty of the results. In addition, knowledge on the acceptability and tolerability of the applied treatments is sparse, but this must be given detailed consideration when dealing with these kinds of treatments.

Implications for research

There is a great need for randomised controlled trials focusing on the short-, medium-, and especially long-term follow-up of participants, where reasons for drop-outs, especially if they are treatment-related, are put into consideration. This includes the importance of examining discontinuation effects in psychopharmacological trials; future prevention trials should collect data on this topic. Also, sample sizes are often small, and need to be larger. More regard should be given to the planning and publication of study protocols. Final publications of study results should report on all study outcomes, especially if they are of interest to the research question. We noted that some studies used generic instruments and cut-offs to measure incidence and severity of depression, but hardly any information was offered on the severity of depression. Here, researchers should be more thorough when reporting outcomes. Overall, the quality of study conduct and reporting needs to improve.

With regard to our outcomes of interest, results were very heterogeneous. In part, this is due to the nature of this review, focusing on so many aspects at once. Still, we would like to recommend future research to focus on corresponding proceedings with prior research instead of attempting new approaches, using different procedures, most of the time. Heterogeneity could be minimised when considering the type of long-term physical conditions, the type of treatment, the classes of antidepressant treatment, the applied dosages, the assessment of incidence of

depression (e.g. diagnosis or cut-off), the time-frames of treatment and follow-up, the used instruments or versions of instruments (e.g. long versions versus short-versions), or the applied cut-offs of the same instrument, for the conduct of future trials. Greater comparability of studies, more care regarding their quality, and larger trials; and specifically in the case of prevention trials, a clear and predefined definition of the type of prevention (primary, secondary or tertiary) that is intended for investigation; can help to improve conclusions drawn from trials and to make well-founded recommendations for clinical practice.

Moreover, future research might consider other proximal outcomes for depression, like risk factors, instead of focusing on depression as the only primary outcome of an RCT. Addressing proxy measures of depression might also prove to be beneficial regarding other methodological problems like high drop-out rates and the need for long follow-up periods. In addition, future research should be much more considerate of the benefit to harms ratio of long-term antidepressant treatment, not only for pharmacological but also for psychological interventions (Herzog 2019; Klatte 2018).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Almeida 2006

Study characteristics	
Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 981
	Method of randomisation: block randomisation
	Method of concealment: centralised
	Blinding: double-blind
	Analysis: intention-to-treat
	Date the study was conducted: June 2002 - June 2004
Participants	**Location**: Australia
	Total N randomised: 111
	Intervention n: 55 (67 % male; age M = 68, SD = 13; haemorrhagic stroke n = 7, Ischaemic stroke n = 104)
	Control n: 56 (63 % male; age M = 67, SD = 13)
	Inclusion criteria: acute Ischaemic or haemorrhagic stroke and no depression at baseline
	Diagnostic criteria - long-term physical condition: acute Ischaemic or haemorrhagic stroke diagnosed according to ICD-10
	Diagnostic criteria - depression: depression is assessed by the HADS - depression sub scale [HADS-D] (a cut-off score > 7 implies depression)
	Exclusion criteria: alcohol dependence; severe communication difficulties (aphasia or limited ability to communicate in English); unstable medical condition as determined by the treating physician; severe cognitive impairment (Mini-Mental State Examination [MMSE] score ≤ 10); and depression (HADS-D score > 7); taking· antidepressants (within 4 weeks of stroke); prior history of clinically significant adverse reactions to sertraline
	History of depression: no information specified
Interventions	**Intervention**: sertraline: fixed daily dose of 50 mg at night
	Control: matched placebo
	Other treatment: intervention/placebo: within a period up to 2 weeks after stroke symptoms became apparent
	Duration of treatment: 24 weeks
	Length of follow-up: 52 weeks after randomisation (at baseline, 12, 24, 36 and 52 weeks)
	Other study arms: No
Outcomes	**Primary outcome**:
	• incidence of depression - diagnosis: diagnosis by the treating physician at 24 or 52 weeks (prescription of an antidepressant)
	• adverse events: total number of adverse events (at 12 or 24 weeks)

Almeida 2006 *(Continued)*

Secondary outcome:

- incidence of depression - cut-off: HADS-D cut-off score ≥ 8 (at 24 or 52 weeks)
- severity of depression: HADS-D (at 24 or 52 weeks)
- cost-effectiveness: N/A
- cost-utility: N/A

Notes	**Language:** English
	Funding: Unrestricted grant from the Rotary Health Research Fund of Australia, Parramatta, Australia. No other financial affiliation is relevant to the subject of this article.
	Declaration of interest: No other financial affiliation is relevant to the subject of this article.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"subjects were allocated ... according to a computer-generated random list of numbers..." (P. 1105) "the lists were produced in random blocks of 8, 10, or 12 subjects to minimize the risk of unbalanced treatment groups and nonblinding" (P. 1105)
Allocation concealment (selection bias)	Low risk	"...according to a computer-generated random list of numbers that was maintained centrally and independently by the pharmacist of the Royal Perth Hospital..." (P. 1105)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	both the research team and participants were unaware of treatment allocation until the final endpoint was collected from the last participant enrolled into the study. (P. 1105)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	both the research team and participants were unaware of treatment allocation until the final endpoint was collected from the last participant enrolled into the study. (P. 1105)
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomise**d: sertraline: n = 55; placebo: n = 56; total: n = 111 **number of drop-outs** at week 24: n = 12, no further information specified **number of drop-outs** at week 52: sertraline: n = 11; placebo: n = 6; total: n = 17 **numbers analysed** post-intervention: sertraline: n = 48; placebo: n = 51; total: n = 99 **numbers analysed** follow-up: sertraline: n = 44; placebo: n = 50; total: n = 94 reasons for drop-out: no further information specified
Selective reporting (reporting bias)	Unclear risk	no protocol available
Other bias	Low risk	"only I breach of protocol was recorded: treatment allocation was disclosed upon request from the treating physician and Ethics Committee after a participant developed seizures. Treatment was discontinued at the end of week 24." (P. 1105)

Hansen 2012

Study characteristics	
Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 11594
	Method of randomisation: centrally prepared randomisation blocks
	Method of concealment: us of the consecutive number of the study medication
	Blinding: double-blind
	Analysis: intention-to-treat
	Date the study was conducted: November 2004 - December 2007
Participants	**Location**: Denmark
	Total N randomised: 240 (one patient was excluded due to protocol violation)
	Intervention n: 120 (63 % male; age M = 65, SD = 12)
	Control n: 119 (63 % male; age M = 64, SD = 12)
	Inclusion criteria: acute coronary syndrome (ACS) and no depression at baseline; age > 18
	Diagnostic criteria - long-term physical condition: diagnosis of ACS based on symptoms, electrocardiogram and cardiac enzymes according to contemporary guidelines
	Diagnostic criteria - depression: depression diagnosis assessed by SCAN interview and confirmation by a psychiatrist
	Exclusion criteria: current depression as determined by a structured interview and confirmed by a psychiatrist; use of antidepressants or antipsychotics; previous intolerance to SSRI; severe, life-threatening medical conditions; severe heart failure; current alcohol or substance abuse, psychosis or dementia; participation in other intervention trials; pregnancy and lactation; linguistic difficulties
	History of mental disorder: Intervention n = 20 (16.7 %); Control n = 18 (15.1 %)
Interventions	**Intervention**: escitalopram
	• ≤ 1 week: daily dose of 5 mg
	• weeks 2 to 52 weeks: daily dose of 10 mg
	Control: matched placebo
	Other treatment: aspirin, clopidogrel, beta-blockers, digoxin, angiotensin-II antagonists, ACE inhibitors, statins, calcium antagonists, long acting nitrates, diuretics, benzodiazepines, hypnotic drugs, antidiabetics, eltroxin and antacids
	Duration of treatment: 12 month
	Length of follow-up: 12 month (at baseline, 2, 8 and approximately 15, 22, 29, 36, 43, and 50 weeks)
	Other study arms: no
Outcomes	**Primary outcome**:
	• incidence of depression - diagnosis: diagnosis according to ICD-10 (moderate or severe) assessed by SCAN interview
	• adverse events: total number of adverse events measured by the Side Effect Rating Scale
	Secondary outcome:

Hansen 2012 *(Continued)*

- incidence of depression - cut-off: N/A
- severity of depression: HDS (note: only baseline means were reported)
- cost-effectiveness: N/A
- cost-utility: N/A

Notes	Patients were screened for depression by study investigators using the HDS at all assessments. In case of positive screening (cut-off score ≥ 13),

- investigator increased the dose of study medication to 20 mg
- patients were seen at an extraordinary visit (approximately 14 days later) by a psychiatrist to diagnose a depressive episode according to ICD-10

Language: English

Funding: The Danish Hearts Foundation (01-1-9-F13-22884), Danish Medical Research Council (22-02-0221) and H. Lundbeck Ltd. The sponsors of the study had no role in study design, manuscript draft or decision to submit the manuscript.

Declaration of interest: The authors declare that they have no competing interests.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization was done in centrally prepared randomization blocs unknown to the investigators." (P. 12)
Allocation concealment (selection bias)	Low risk	"the allocation sequence was implemented using the consecutive number of the study medication." (P. 12)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"investigators, nurses, outcome assessors as well as included patients remained blinded to group assignment during the entire intervention and data analysis." (p.12)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"investigators, nurses, outcome assessors as well as included patients remained blinded to group assignment during the entire intervention and data analysis." (p.12)
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: escitalopram: n = 120; placebo: n = 120; total: N = 240 note: n = 1 participant was excluded due to protocol violation; total: N = 239 **number of drop-outs** at 12 months: escitalopram: n = 35; placebo: n = 30; total: N = 65 **numbers analysed** post-intervention: escitalopram: n = 85; placebo: n = 89; total: N = 174 reasons for drop-out: • "among the 65 (27.2%) patients who did not complete the study period, 55 (23%) withdrew their consent or dropped out within the first 6 months (28 patients within first 4 weeks). No significant differences between treatment groups in the number or the time for treatment stop were found" (P. 13) • "during the study period there were no serious adverse events related to study medication. Four patients (1.7%) died while still on trial medication, 3 in the escitalopram group and 1 in the placebo group (P = 0.62). Among the 13 patients withdrawing from the study due to possible side effects, 8 were in treatment with escitalopram and 5 with placebo (P = 0.61)" (P. 14)

Hansen 2012 *(Continued)*

		• no further information specified
Selective reporting (reporting bias)	High risk	protocol available
		• only one of the two pre-specified primary outcomes was reported; no information on HDS scores except for dosage increase of medication due to HDS ≥ 13 (N = 9)
		• no further information specified on side effects: "The incidence of most of the 48 symptoms contained in the UKU side effect scale did not differ between groups, and no single symptom was more common in any group for more than one visit." (P. 14)
		• "1 patient excluded du to protocol violation" (fig.1, P. 13)
Other bias	Low risk	no

Hansen 2014

Study characteristics

Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 703
	Method of randomisation: random assignment in blocks of six based on a list that was computer generated
	Method of concealment: centralised
	Blinding: double-blind
	Analysis: intention-to-treat
	Date the study was conducted: July 2011 - December 2012
Participants	**Location**: Denmark
	Total N randomised: 54
	Intervention n: 28 (0 % male; age M = 51, range = 46 - 66)
	Control n: 26 (0 % male; age M = 60, range = 49 - 68)
	Inclusion criteria: women; age 30-75 years; breast cancer
	Diagnostic criteria - long-term physical condition: scheduled for lumpectomy or mastectomy for breast cancer, with American Society of Anesthesiologists (ASA) class 1-lll
	Diagnostic criteria - depression: MDI cut-off score ≥ 21
	Exclusion criteria: signs of depression on the Major Depression Inventory (MDI); pregnancy; neoadjuvant chemotherapy; treatment with selective serotonin reuptake inhibitors, antithrombotic drug therapy (except 75 mg acetylsalicylic acid daily), monoaminoxidase (MAO) inhibitors, calcium channel blockers, rotor or Dubine Johnson syndrome; epilepsy; known allergic reaction to melatonin; known and treated sleep apnoea; diabetes mellitus treated with insulin; ongoing or previous medically treated depression or bipolar disorder; known autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis or only sclerosis); incompensated liver cirrhosis; severe kidney disease (receiving dialysis); previous or other current cancer; known medically treated sleep disorder (insomnia, restless legs, etc.); shift work or night work; daily intake of > 5 units (1 unit = 8 g pure alcohol); preoperative continuous treatment with psychopharmacological drugs of any kind, opioids, anxiolytics or hypnotics; predicted poor compliance; breast feeding; preoperative Mini Mental State Examination score < 24

Hansen 2014 *(Continued)*

	History of depression: no
Interventions	**Intervention**: daily dose of 6 mg melatonin 1h before bedtime (1 week preoperatively and 12 weeks postoperatively)
	Control: matched placebo
	Duration of treatment: 13 weeks
	Length of follow-up: 13 weeks (at 1 week preoperatively, baseline, 2, 4, 8, 12 weeks)
	Other study arms: no
Outcomes	**Primary outcome**: • incidence of depression - diagnosis: N/A • adverse events: total number of adverse events **Secondary outcome**: • incidence of depression - cut-off: MDI cut-off score ≥ 21 • severity of depression: N/A • cost-effectiveness: N/A • cost-utility: N/A
Notes	**Language:** English **Funding:** grants from The University of Copenhagen, The Aase and Ejnar Danielsens Foundation, The A.P. Møller Foundation for the Advancement of Medical Science, The Else and Mogens Wedell Wedell-borgs Foundation, The Beckett Foundation, The Hede Nielsen Family Foundation, The Dagmar Marshalls Foundation and Manufacturer Einar Willumsen's Memorial Scholarship **Declaration of interest:** none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"on inclusion patients were randomly assigned, in blocks of six, to melatonin or placebo" (p. 684) "the randomisation list was computer generated using dedicated software (http://www.randomization.com)" (p. 684)
Allocation concealment (selection bias)	Low risk	"this procedure was completed by the hospital pharmacy, who received the medicine directly from Pharma Nord. The pharmacy packed the melatonin/placebo in identical, sequentially numbered, sealed boxes" (p. 684)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"the participants, the health care providers, the research staff... were all blinded to allocation and the allocation sequence by taking the sequentially numbered sealed boxes" (p. 684)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... and the investigators assessing the outcomes were all blinded to allocation and the allocation sequence by taking the sequentially numbered sealed boxes" (p. 684)
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: melatonin: n = 28; placebo: n = 26; total: N = 54

Hansen 2014 *(Continued)*

		number of drop-outs at 3 months: melatonin: n = 1; placebo: n = 10; total: N = 11
		numbers analyzed post-intervention: melatonin: n = 27; placebo: n = 16; total: N = 43
		reasons for drop-out (p. 692):
		melatonin: unable to cope with participation in trial
		placebo: adverse events, noncompliance, lost to follow-up, unable to cope with participation in trial
Selective reporting (reporting bias)	High risk	protocol available
		outcomes on e.g. cognitive function have not been reported
		"were tested with the neuropsychological test battery (data not reported here)" (p. 684)
Other bias	Low risk	"...the only change after trial commencement was that the upper limit of the age criteria was raised from 70 to 75 years on 19 October 2011, because of slow recruitment" (p. 684)
		"patients were recruited from July 2011- to December 2012 where the trial was terminated prematurely (n = 54) due to restructuring of surgery for breast cancer in the region resulting in an overall low inclusion rate. We tried to include other centres in other regions, but this was not possible because of lack of funding" (p. 692)

Lydiatt 2008

Study characteristics	
Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 75
	Method of randomisation: coin toss, randomisation ratio 1:1
	Method of concealment: no information specified
	Blinding: double-blind (participants and all investigators)
	Analysis: intention-to-treat
	Date the study was conducted: July 2002 - April 2005
Participants	**Location**: USA
	Total N randomised: 36 (among these n = 5 with baseline depression, and n = 1 who failed Mini Mental State Examination)
	Randomised and Eligible: 30 (among these n = 2 who failed to show-up for allocation and baseline visit)
	Randomised and Allocated: 28
	Intervention n: 15
	demographics are only available for those participants who completed visit one after 4 weeks
	n = 13 (62 % male; age M = 61, range 43 - 81)

Lydiatt 2008 *(Continued)*

	Control n: 13 demographics are only available for those participants who completed visit one after 4 weeks n = 12 (33 % male; age M = 61, range 48 - 76) **Inclusion criteria**: newly diagnosed or recurrent cancers of the oral cavity, larynx, pharynx, neck, or paranasal sinuses requiring more than limited excision; age ≥ 19 **Diagnostic criteria - long-term physical condition**: newly diagnosed or recurrent cancers of the oral cavity, larynx, pharynx, neck, or paranasal sinuses requiring more than limited excision; assessment not specified **Diagnostic criteria - depression**: depression diagnosis according to DSM-IV assessed by the MINI **Exclusion criteria**: meeting diagnostic criteria for major depressive disorder; cognitive impairment (MMSE score ≤ 24); use of antidepressant medication; contraindication to citalopram; meeting diagnostic criteria for psychosis or schizophrenia; suicidal tendencies **History of depression:** no information specified
Interventions	**Intervention**: citalopram hydrobromide • ≤ 1 week: daily dose of 20 mg • weeks 2 to 11: daily dose of 40 mg • week 12: daily dose of 20 mg • > week 12: no further use of study medication **Control**: matched placebo **Other treatment**: conventional cancer therapy according to the National Comprehensive Cancer Network Guidelines (surgery, radiation therapy with and without chemotherapy) **Other possible treatment**: supportive care and support group (no psychotherapy and antidepressants) **Duration of treatment**: 12 weeks **Length of follow-up**: 16 weeks (at baseline, 4, 8, 12 and 16 weeks) **Other study arms:** yes Due to an error, five ineligible participants with depression at baseline were randomised. "Subjects with HDRS scores of at least 15 at baseline were continued in the study because data on the treatment vs the natural history of untreated MDD have also not been studied in HNC. They were excluded from the primary analysis of MDD prevention because, by definition, MDD was already present." (p. 530)
Outcomes	**Primary outcome**: • incidence of depression - diagnosis: diagnosis according to DSM-IV assessed by MINI module depression (at baseline, 4, 8, 12 and 16 weeks) • adverse events: total number of drop-outs due to adverse events **Secondary outcome**: • incidence of depression - cut-off: HRSD cut-off score ≥ 15 (at baseline, 4, 8, 12 and 16 weeks) (note: we only reported the primary outcome: incidence of depression assessed by diagnosis) • global assessment of severity of depression: CGI-S (at baseline, 4, 8, 12 and 16 weeks) • cost-effectiveness: N/A • cost-utility: N/A
Notes	**Language:** English

Lydiatt 2008 *(Continued)*

Funding: University of Nebraska Clinical Research Center and an unrestricted grant from Ted Kooser. Forest Laboratories Inc provided matching drug and placebo.

Declaration of interest: Dr Burke has served as a consultant and received honoraria and research support from Forest Laboratories Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"subjects were randomised in the University of Nebraska pharmacy by coin toss in a 1:1 fashion to receive placebo or citalopram" (p. 529)
Allocation concealment (selection bias)	Low risk	"subjects were randomised in the University of Nebraska pharmacy" (p. 529)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"all assessments were performed in a blinded fashion. Neither the investigators nor the subjects knew whether they were receiving active drug or placebo." (p. 530)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"all assessments were performed in a blinded fashion. Neither the investigators nor the subjects knew whether they were receiving active drug or placebo." (p. 530)
Incomplete outcome data (attrition bias) All outcomes	High risk	pre-randomisation: • due to an error, six ineligible participants (five with depression at baseline and one with a low MMSE score) were randomised but excluded from any analyses; • another two participants did not show up for allocation and baseline visit **numbers randomised**: citalopram: n = 15; placebo: n = 13; total: N = 28 **number of drop-outs** at 16 weeks: citalopram: n = 2; placebo: n = 3; total: N = 5 **numbers analysed** post-intervention: citalopram: n = 13; placebo: n = 10; total: N = 23 reasons for drop-out (fig. 1, p. 530): citalopram: adverse events placebo: decision to withdraw, placement in care facility, or hospitalisation for depression
Selective reporting (reporting bias)	Unclear risk	no protocol available
Other bias	Unclear risk	data on demographics is only available for those participants who completed visit one after 4 weeks

Lydiatt 2013

Study characteristics

Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 298

Lydiatt 2013 *(Continued)*

Method of randomisation: 1:1 ratio according to a randomisation table prepared by the study statistician

Method of concealment: centralised

Blinding: double-blind

Analysis: per protocol

Date the study was conducted: January 2008 - December 2011

Participants	**Location**: USA

Total N randomised: 148

Intervention n: 74 (80 % male; age M = 63, SD = 11)

Control n: 74 (80 % male; age M = 63, SD = 13)

Inclusion criteria: > 18 years; newly diagnosed or recurrent stage II to IV epidermoid cancer of the head and neck

Diagnostic criteria - long-term physical condition: newly diagnosed or recurrent stage II to IV epidermoid cancer of the head and neck (no assessment specified)

Diagnostic criteria - depression:

- depression diagnosis assessed by the MINI depression and suicide modules;
- clinician version of the QIDS (QIDS-C): QIDS-SR cut-off score ≥ 11

Exclusion criteria: cognitively impaired; advanced cancer or other conditions that limited life expectancy to less than 6 months; met diagnostic criteria for psychosis, schizophrenia, or major depressive disorder; receiving treatment for depression or anxiety; persistent inability to verbally communicate; uncontrolled pain; currently participating in another research study involving a therapeutic intervention; were females of childbearing age who were pregnant, nursing, or not practicing a reliable method of birth control

History of depression: no information specified

Interventions	**Intervention**: escitalopram

- ≤ 1 week: daily dose of 10 mg
- weeks 1-15: daily dose of 20 mg
- week 16: daily dose of 10 mg

Control: matched placebo

Duration of treatment: 16 weeks

Length of follow-up: 28 weeks (baseline, at 2, 4, 6, 8, 10, 12, 16, 20, 24, and 28 weeks)

Other study arms: no

Outcomes	**Primary outcome**:

- incidence of depression - diagnosis: N/A
- adverse events: total number of drop-outs due to adverse events

Secondary outcome:

- incidence of depression - cut-off: QIDS-SR cut-off score ≥ 11
- severity of depression: N/A
- cost-effectiveness: N/A

Lydiatt 2013 *(Continued)*

- cost-utility: N/A

Notes	**Language:** English
	Funding: grant R01 MH079420 from the National Institute of Mental Health additional support was provided by a research support fund grant from the Nebraska Medical Center and the UNMC
	Declaration of interest: Dr Lydiatt is on the head and neck panel for guideline development for the National Comprehensive Cancer Network but does not receive honorarium for participation in guideline development. Dr Burke has received grant support for his institution from Forest Research Institute and has served as a consultant to Forest and on their speakers' bureau.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...patients were randomised by a pharmacist with no involvement in the evaluation in a 1:1 ratio to either escitalopram or matching placebo according to a randomisation table prepared by the study statistician" (p. 680)
Allocation concealment (selection bias)	Low risk	"patients were randomised by a pharmacist with no involvement in the evaluation ..." (p. 680)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	no information specified except for headline saying "...double-blind ..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	no information specified except for headline saying "...double-blind ..."
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: escitalopram: n = 74; placebo: n = 74; total: N = 148
		number of drop-outs at 28 weeks: escitalopram: n = 38; placebo: n = 30; total: N = 68
		numbers analysed post-intervention: escitalopram: n = 36; placebo: n = 44; total: N = 80
		reasons for drop-out (p. 681, fig. 1)
		escitalopram:
		• non-evaluable (only baseline visit): adverse events, withdrew consent, need to take lorazepam, fear of adverse events, surgical complications
		• evaluable: adverse events, withdrew consent, unable to take medication in nursing home, recommendation to stop study by primary physician, death
		placebo:
		• non-evaluable (only baseline visit): adverse events, withdrew consent, did not want to take medication
		• evaluable: adverse events, withdrew consent, unable to take medication in nursing home, need to take lorazepam, wants to continue to take antidepressant
Selective reporting (reporting bias)	Unclear risk	no protocol available

Lydiatt 2013 *(Continued)*

Other bias	Unclear risk	"patients were stratified by site (UNMC or NMCC), sex, stage (early [stage II] vs advanced [stage III/IV]), and primary modality of treatment (radiation with or without chemotherapy vs surgery [not biopsy] with or without radiation)" (p. 679)

Narushima 2002

Study characteristics

Methods	**Study design**: randomised (3-arm parallel randomised controlled clinical trial) **Sample size:** 347 (USA: 343; Argentina: 4) **Method of randomisation**: no information specified **Method of concealment**: no information specified **Blinding**: double-blind **Analysis**: intention-to-treat **Date the study was conducted:** July 1991 - June 1997
Participants	**Location**: USA and Argentina **Total N randomised**: 48 **Intervention n**: 32 • fluoxetine 17 (88% male; no information on age available) • nortriptyline 15 (47% male; no information on age available) **Control n**: 16 (75 % male; no information on age available) **Inclusion criteria**: thromboembolic stroke or intracerebral haemorrhage; no depression at baseline; age 18-85 **Diagnostic criteria - long-term physical condition**: thromboembolic stroke or intracerebral haemorrhage (assessed by neurologists or neuroradiologists who evaluated computerized tomography or magnetic resonance scans) **Diagnostic criteria - depression**: depression diagnosed according to DSM-IV assessed by the PSE **Exclusion criteria**: severe comprehension deficit (unable to answer correctly part 1 of the token test); use of antidepressant; contraindication to nortriptyline or fluoxetine; acute stroke (within 6 month of study entry) **History of depression:** no information specified
Interventions	**Intervention**: fluoxetine • ≤ 3 weeks: daily dose of 10 mg • weeks 4 to 6: daily dose of 20 mg • weeks 7 to 9: daily dose of 30 mg • weeks 10-12: daily dose of 40 mg nortriptyline • ≤ 1 week: daily dose of 25 mg

Narushima 2002 *(Continued)*

- weeks 2 and 3: daily dose of 50 mg
- weeks 3 to 6: daily dose of 75 mg
- weeks 6 to 12: daily dose of 100 mg

Control: matched placebo

Duration of treatment: 3 months

Length of follow-up: 24 month (at baseline, 3, 6, 9, 12, and 24 months)

[no follow-up for participants from Argentina (duration of participation: 3 months)]

Other study arms: no

Outcomes	**Primary outcome**: - incidence of depression - diagnosis: diagnosis according to DSM-IV assessed by the PSE - adverse events: N/A **Secondary outcome**: - incidence of depression - cut-off: N/A - severity of depression: HAM-D-17 (means were not reported but presented in a figure) - cost-effectiveness: N/A - cost-utility: N/A
Notes	Decreasement of medication in case of severe side effects **Language:** English **Funding:** National Institute of Mental Health Grants MH-40355, MHH-52879, MH-53592 and Research Scientist Award MH-00163 (RGR) **Declaration of interest:** no information specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no information specified "Patients were randomly assigned to 12 weeks of treatment with fluoxetine, nortriptyline, or placebo unless one of the active drugs was contraindicated. Nortriptyline was contraindicated in patients with cardiac conduction abnormalities, and fluoxetine was contraindicated in patients with intracerebral hemorrhage. Of the 48 nondepressed patients, 7 had a contraindication to nortriptyline and 5 had a contraindication to fluoxetine. These patients were randomly assigned to receive noncontraindicated medication or placebo. Thus, 75% of the patients were randomly assigned to nortriptyline or fluoxetine, whereas all patients were randomly assigned to active or placebo medication."
Allocation concealment (selection bias)	Unclear risk	no information specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The effectiveness of the blind was determined by asking patients and raters to guess whether they were taking active or placebo medication. For active medication, patients were correct 59 % and raters 65 % of the time. For placebo, patients were correct 55 % and raters 46 % of the time. There was no statistically significant difference from a random distribution of guesses for either patients or raters." (p. 298)

Narushima 2002 *(Continued)*

		While blinding for participants and outcome assessment received low risk of bias ratings, further study personnel appeared to be aware of study allocation: "Doses were decreased if side effects were severe, which was the case for six nondepressed patients. Of these six patients, four were treated with nortriptyline and two with fluoxetine. To maintain the double-blind design, doses were decreased for equal numbers of placebo patients. Nortriptyline-treated patients were monitored for serum drug concentrations throughout the treatment period to adjust the drug level within the therapeutic window."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The effectiveness of the blind was determined by asking patients and raters to guess whether they were taking active or placebo medication. For active medication, patients were correct 59 % and raters 65 % of the time. For placebo, patients were correct 55 % and raters 46 % of the time. There was no statistically significant difference from a random distribution of guesses for either patients or raters." (p. 298)
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: fluoxetine: n = 17; nortriptyline: n = 15; placebo: n = 16; total: N = 48 **number of drop-outs** at 3 months: fluoxetine: n = 2; nortriptyline: n = 2; placebo: n = 1; total: N = 5 **numbers analysed** post-intervention: fluoxetine: n = 15; nortriptyline: n = 13; placebo: n = 15; total: N = 43 reasons for drop-out (pp. 298-299): fluoxetine: gastrointestinal symptoms, refused treatment (note: the authors initially name n = 4 drop-outs for the treatment study, however, among these n = 2 who became depressed, and therefore are not considered drop-outs for the prevention task but incidence events); nortriptyline: sedative effects, refused treatment placebo: rash
Selective reporting (reporting bias)	Unclear risk	no protocol available
Other bias	High risk	• "Patients were randomly assigned to 12 weeks of treatment with fluoxetine, nortriptyline, or placebo unless one of the active drugs was contraindicated. Nortriptyline was contraindicated in patients within cardiac conduction abnormalities, and fluoxetine was contraindicated in patients with intracerebral hemorrhage. Of the 48 nondepressed patients, 7 had a contraindication to nortriptyline and 5 had a contraindication to fluoxetine. These patients were randomly assigned to receive noncontraindicated medication or placebo. Thus, 75 % of the patients were randomly assigned to nortriptyline or fluoxetine, whereas all patients were randomly assigned to active or placebo medication" (p. 297) • no information on baseline characteristics, e.g. age • no declaration of interest

Novack 2009

Study characteristics

Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)

Novack 2009 *(Continued)*

	Sample size: 371
	Method of randomisation: no information specified
	Method of concealment: no information specified
	Blinding: double-blind
	Analysis: intention-to-treat
	Date the study was conducted: no information specified
Participants	**Location**: USA
	Total N randomised: 99
	Intervention n: 49 (79 % male; age M = 35, SD = 17)
	Control n: 50 (66 % male; age M = 35, SD = 16)
	Inclusion criteria: within 8 weeks of injury (= traumatic brain injury); injury sufficient to require inpatient rehabilitation; age 19-75
	Diagnostic criteria - long-term physical condition: traumatic brain injury: Glasgow Coma Scale (GCS) score of ≤ 12, or neuroimaging results consistent with the effects of trauma (e.g., contusion, subdural hematoma) at admission
	Diagnostic criteria - depression: diagnosis according to DSM-IV assessed by SCID-I
	Exclusion criteria: existing neurological difficulties; use of antidepressant medication at the time of injury; administration of antidepressant medication in the hospital prior to enrolment; ongoing steroid treatment; depression necessitating treatment at the time of enrolment; pregnancy, alcohol or drug abuse in the year prior to the injury; systemic medical illnesses that would independently limit outcome (such as severe renal disease and cardiac difficulties)
	History of depression: no
Interventions	**Intervention**: daily dose of 50 mg sertraline
	Control: placebo
	Duration of treatment: 3 months
	Length of follow-up: 12 months (3, 6, and 12 months)
	Other study arms: no
Outcomes	**Primary outcome**:
	• incidence of depression - diagnosis: diagnosis according to DSM-IV assessed by SCID-I • adverse events: N/A
	Secondary outcome:
	• incidence of depression - cut-off: HDRS cut-off score ≥ 8; HDRS cut-off score ≥ 6 (note: we only reported the primary outcome: incidence of depression assessed by diagnosis) • severity of depression: NFI • cost-effectiveness: N/A • cost-utility: N/A
Notes	**Language:** English
	Funding: National Institute of Disability and Rehabilitation Research Grant H133A980010 Traumatic Brain Injury Model System Project

Novack 2009 *(Continued)*

Declaration of interest: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no information specified
Allocation concealment (selection bias)	Unclear risk	no information specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"If depression was confirmed, the blind was broken for the treating physician, but not for the psychometrician performing the outcome assessments" (p. 1923)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"If depression was confirmed, the blind was broken for the treating physician, but not for the psychometrician performing the outcome assessments" (p. 1923)
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: sertraline: n = 49; placebo: n = 50; total: N = 99 **number of drop-outs** at 3 months: sertraline: n = 1; placebo: n = 2; total: N = 3 **number of drop-outs** at 12 months: sertraline: n = 13; placebo: n = 14; total: N = 27 **numbers analysed** post-intervention at 3 months: sertraline: n = 48; placebo: n = 48; total: N = 96 **numbers analysed** at follow-up at 12 months: sertraline: n = 36; placebo: n = 36; total: N = 72 reasons for drop-out (p. 1926): sertraline: stopped taking study meds, lost or withdrew, O-Log < 25 or nursing home, adverse events, expired placebo: stopped taking study meds, lost or withdrew, O-Log < 25 or nursing home, expired
Selective reporting (reporting bias)	Unclear risk	no protocol available
Other bias	Low risk	no

Rasmussen 2003

Study characteristics

Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 155
	Method of randomisation: division in terms of gender and age (over and under 65 years of age)
	Method of concealment: no information specified

Rasmussen 2003 *(Continued)*

Blinding: double-blind

Analysis: no information specified

Date the study was conducted: January 1996 - May 1998

Participants	**Location**: Denmark
	Total N randomised: 137
	Intervention n: 70 (50 % male; age M = 72, SD = 9)
	Control n: 67 (51 % male; age M = 68, SD = 11)
	Inclusion criteria: stroke in the preceding 4 weeks
	Diagnostic criteria - long-term physical condition: stroke is diagnosed according to clinical criteria (WHO)
	Diagnostic criteria - depression: diagnosis of depression according to ICD-10 and assessed by clinical interview
	Exclusion criteria: current depression (total score > 13 on the HAM-D-17); stroke occurrence not with-in the preceding four weeks; significant aphasia; use of antidepressants (within the preceding 4 weeks); dementia; history of schizophrenia, psychosis, or severe drug abuse; present preexisting neurological illness; cardiovascular illness (within preceding 6 months)
	History of depression: no information specified
Interventions	**Intervention**: daily dose of 50 mg sertraline (in case of clinical need, dosage is flexibly increased up to a maximum dose of 150 mg/day)
	Control: matched placebo
	Duration of treatment: 12 months
	Length of follow-up: 12 months (at baseline, and 11 post-randomisation visits (occurring at approxi-mately 4-5 week intervals)
	Other study arms: no
Outcomes	**Primary outcome**:
	• incidence of depression - diagnosis: N/A
	• adverse events: total numbers of adverse events measured by the UKU Side Effect Rating Scale
	Secondary outcome:
	• incidence of depression - cut-off:
	○ HAM-D (modified 17-item version with item 14 sexual behaviour not rated) cut-off score > 18 (at baseline, 3, 6 and 11 months);
	○ HAM-D (6-item version) cut-off score ≥ 9 (at baseline, 3, 6 and 11 months);
	○ GDS cut-off score > 16 (at baseline and all post-randomisation visits)
	(Note: due to the predefined hierarchy of outcome measures we used data from the HAM-D 17-item ver-sion when reporting the incidence of depression.)
	• severity of depression: Newcasatle II scale (at baseline, 2, and 4 months) but not reported
	• cost-effectiveness: N/A
	• cost-utility: N/A
Notes	**Language:** English
	Funding: Pfizer A/S, Gert Jørgensen legat, and the Brain Cause (Hjernesagen)

Rasmussen 2003 *(Continued)*

Declaration of interest: no information specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were fairly evenly divided in terms of gender and those over versus under 65 years of age..." (p. 218)
Allocation concealment (selection bias)	Unclear risk	no information specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	no information specified except for headline and p. 217 saying "...double-blind ..."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	no information specified except for headline and p. 217 saying "...double-blind ..."
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: sertraline: n = 70; placebo: n = 67; total: N = 137 **number of drop-outs** at 12 months: sertraline: n = 9; placebo: n = 10; total: N = 19 **numbers analysed** post-intervention: sertraline: n = 61; placebo: n = 57; total: N = 118 reasons for drop-out: no information specified
Selective reporting (reporting bias)	High risk	no protocol available but not all outcomes were reported, e.g. Newastle II scale
Other bias	Low risk	no

Robinson 2008

Study characteristics

Methods	**Study design**: 3-arm parallel randomised controlled clinical trial (note: the third study-arm problem-solving therapy was not extracted due to no suitable control group) **Sample size:** 200 **Method of randomisation**: permuted blocks randomisation scheme; sample size randomly divided into block sizes of 3, 6, and 9; within each block random assignment to numbers of 1, 2, or 3 (the three treatment arms) **Method of concealment**: centralised **Blinding**: double-blind **Analysis**: intention-to-treat **Date the study was conducted:** July 2003 - October 2007
Participants	**Location**: USA

Robinson 2008 *(Continued)*

Total N randomised: 176 but we excluded the third study-arm problem-solving therapy (n = 59) resulting in N = 117

Intervention n: 59 (64 % male; age M = 61, SD = 14)

Control n: 58 (64 % male; age M = 64, SD = 13)

Inclusion criteria: no depression at baseline; hemispheric, brainstem, or cerebellar (including Ischaemic or haemorrhagic) stroke in the preceding 3 moths; age 50-90

Diagnostic criteria - long-term physical condition: stroke is diagnosed by clinical and neurological findings consistent with either hemispheric, brainstem, or cerebellar stroke

Diagnostic criteria - depression: depression is diagnosed according to DSM-IV and assessed by the HAM-D (17-item version; a cut-off score > 11 implies depression)

Exclusion criteria: severe comprehension deficits (inability to complete part 1 of the Token Test); impaired
decision-making capacity (neuropsychological testing); alcohol or substance abuse or dependence according to DSM-IV (within the last past 12 months); acute coronary syndromes; neurodegenerative disorders; life-threatening heart or respiratory failure; renal or hepatic failure; severely disabling musculoskeletal disorder; cancer, and neurodegenerative disorders such as idiopathic Parkinson disease or Alzheimer disease; occurrence of stroke secondary to complications from an intracranial aneurysm, arterial-venous malformation, intracranial tumour or neoplastic process; stroke during the course of myocardial infarction, aortic dissection, or revascularization surgery; stroke due to complications of an intracranial aneurysm, arteriovenous malformation, or neoplastic disease

History of depression:

- intervention: n = 3
- placebo: n = 3

Interventions	**Intervention**: escitalopram:

- < 65 years: daily dose of 10 mg at morning
- ≥ 65 years: daily dose of 5 mg at morning

Control: matched placebo

Duration of treatment: 12 months

Length of follow-up: 18 months (at baseline, 3, 6, 9, 12, and 18 months)

Other study arms: problem-solving therapy

- 6 treatment sessions (weeks 1, 2, 3, 4, 6, and 10) and 6 reinforcement sessions (16, 20, 24, 28, 32, 40, and 48 weeks)
- n = 59 (51 % male; age = 67, SD = 11)

Outcomes	**Primary outcome**:

- incidence of depression - diagnosis: diagnosis according to DSM-IV assessed by SCID-I
- adverse events: total numbers of adverse events measured by a standardized checklist developed for the study

Secondary outcome:

- incidence of depression - cut-off: HDRS-17 cut-off score >12 (note: we only reported the primary outcome: incidence of depression assessed by diagnosis)
- severity of depression: HDRS-17
- cost-effectiveness: N/A
- cost-utility: N/A

Notes	**Language:** English
	Funding: National Institute of Mental Health (NIMH) grant R01 MH-65134; NIMH grant funds were use to purchase all of study medications. All of the authors received salary contributions from the grant supporting this study. Over the past five years, Dr Robinson reports serving as a consultant to the former Hamilton Pharmaceutical Company and Avanir Pharmaceutical Company; receiving support or honoraria from Lubeck, Forest Laboratories, and Pfizer; being on the speakers' bureau for Forest Laboratories and Pfizer; and receiving grant support from the National Institute of Mental Health. Dr Small reports that he conducted a research study funded by Northstar Neuroscience that was unrelated to this prevention study. Dr Arndt reports inheriting Pfizer stock, which he owned from January 6, 2005, to December 23, 2006, and receiving grant support from the National Institute of Mental Health. The former Hamilton Pharmaceutical Company and Avanir Pharmaceutical Company had no financial interest in this prevention study.
	Declaration of interest: no other authors reported any financial disclosures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...using a permuted blocks randomisation scheme Specifically, at the beginning of the study, the targeted sample size was divided randomly (200 patients) into block sizes of 3, 6, and 9 and within each block patients were randomly assigned 1 of the 3 treatments using computer-generated random numbers of 1, 2, or 3..." (p. 4)
Allocation concealment (selection bias)	Low risk	"patients were centrally randomised...by a team member who was not involved in any evaluation..." (p. 4)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	low risk for escitalopram: "the examiners were unaware of each patient's treatment assignment and double-blinded assessments were done for escitalopram and placebo" (p. 5)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	no information specified
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: escitalopram: n = 59; placebo: n = 58; total: N = 117 **number of drop-outs** at 12 months: escitalopram: n = 7; placebo: n = 5; total: N = 12 **number of drop-outs** at 18 months: escitalopram: n = 25; placebo: n = 25; total: N = 50 (note: no information specified, drop-outs were calculated by comparing the data of the two corresponding publications conducted by Robinson 2008 and Mikami 2011). **numbers analyzed** post-intervention at 12 months: escitalopram: n = 52; placebo: n = 53; total: N = 105 **numbers analysed** at follow-up 18 months: escitalopram: n = 34; placebo: n = 33; total: N = 67 reasons for drop-out: at 12 months (p. 14): escitalopram: death, intercurrent disease, could not be reached, protocol violation; placebo: could not be reached, adverse events, intercurrent disease, protocol violations

Robinson 2008 *(Continued)*

		at 18 months (Mikami et al. 2011): escitalopram: no information specified; placebo: no information specified
		note: Even though Mikami et al. 2011 published further data (12 months to 18 months) on the study conducted by Robinson et al. 2008, analyses were conducted independently from preceding results. Information on drop-outs between 12 and 18 months are not available. Information on depression scores of the re-evaluated sub-sample are also not available.
Selective reporting (reporting bias)	High risk	no protocol available; trial registration included the Stroke Impact Scale which was not reported on
Other bias	Low risk	no

Rovner 2007

Study characteristics

Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 602
	Method of randomisation: random-numbers table and fixed randomisation scheme with a 1:1 allocation ratio; permuted random block design; block sizes of 4 or 6 chosen at random, to mask the blocking process
	Method of concealment: sealed envelopes containing treatment assignments
	Blinding: single-blind
	Analysis: intention-to-treat
	Date the study was conducted: December 2001 - July 2005
Participants	**Location**: USA
	Total N randomised: 206
	Intervention n: 105 (34 % male; age M = 81, SD = 5)
	Control n: 101 (26 % male; age M = 81, SD = 6)
	Inclusion criteria: preexisting age-related macular degeneration and neovascular age-related macular degeneration in the other eye; age > 64
	Diagnostic criteria - long-term physical condition: age-related macular degeneration is diagnosed by ophthalmologists' dictated reports of fluorescein angiograms and ophthalmologists' confirmation of diagnosis
	Diagnostic criteria - depression: diagnosis according to DSM-IV criteria
	Exclusion criteria: diagnosis of a depressive disorder according to DSM-IV; current treatment for depression; cognitive impairment; confounding eye conditions
	History of depression:
	• Intervention: 3.4 % • Control: 1.5 %
Interventions	**Intervention**: problem solving therapy delivered in 6 in-home sessions (45-60 minutes long)

Rovner 2007 *(Continued)*

	Control: TAU
	Other treatment: -
	Duration of treatment: 2 months
	Length of follow-up: 2 months (at baseline, 2, and 6 months)
	Other study arms: no

Outcomes	**Primary outcome**:
	• incidence of depression - diagnosis: DSM-IV defined diagnosis of a depressive disorder assessed by the SADS
	• adverse events: N/A
	Secondary outcome:
	• incidence of depression - cut-off: N/A (a HDRS-24 cut-off score ≥ 7 was used to quantify depressive symptoms but data was not reported on)
	• severity of depression: N/A (but comparisons of mean changes of HDRS scores were included)
	• cost-effectiveness: N/A
	• cost-utility: N/A

Notes	**Language:** English
	Funding: Grant RO1 MH61331 from the National Institute of Mental Health; grant U01 EY 015839 from the National Eye Institute; Farber Institute for Neurosciences of Thomas Jefferson University
	Declaration of interest: none reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"to obtain the sample, we reviewed ophthalmologists' dictated reports of fluorescein angiograms, confirmed diagnoses with treating ophthalmologists, and contacted potential subjects...this method of ascertainment was objective and verifiable, avoided relying on ophthalmologists to identify eligible cases, and prevented other selection biases" (p. 887)
		"we used a random-numbers table, sealed envelopes containing treatment assignments, and a fixed randomisation scheme with a 1:1 allocation ratio to assign subjects to 1 of the 2 study groups. We used a permuted random block design to ensure balance between treatment groups according to their time of patient enrolment. Block sizes (4 or 6) were chosen at random to mask the blocking process." (p. 887)
Allocation concealment (selection bias)	Low risk	"...sealed envelopes containing treatment assignments" (p. 887)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"personnel masked to treatment assignment completed central data collection, measurement, and data entry. Only the project director, statistician, and PST therapists were aware of treatment assignment. Following randomisation, the research nurses instructed all subjects on the purpose and importance of masked treatment assignment and requested that subjects not reveal any information about their study participation. We assessed rates of breaches in masking and found that unmasking occurred in 26 PST and 11 control subjects (18.0%). In all instances, subjects inadvertently revealed their treatment assignment. We compared depression rates in unmasked and masked subjects

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Rovner 2007 *(Continued)*

		to determine whether unmasking influenced rates of diagnosing depression and found no difference (P=.80)." (p. 888)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"the outcome assessors were unaware of subjects' treatment assignment in this single masked study." (p. 887)
		"personnel masked to treatment assignment completed central data collection, measurement, and data entry" (p. 888)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	**numbers randomised**: problem solving therapy: n = 105; TAU: n = 101; total: N = 206
		number of drop-outs at 2 months: problem solving therapy: n = 10; TAU: n = 2; total: N = 12
		number of drop-outs at 6 months: problem solving therapy: n = 10; TAU: n = 6; total: N = 16
		numbers analysed post-intervention at 2 months: problem solving therapy: n = 95; TAU: n = 99; total: N = 194
		numbers analysed follow-up at 6 months weeks: problem solving therapy: n = 95; TAU: n = 95; total: N = 190
		reasons for drop-out (p. 887):
		problem solving therapy: loss of interest, too ill, death
		TAU: loss of interest, too ill, death
		Note: drop-outs for the intervention group were reported incorrectly: the authors state that 11 subjects in the problem-solving therapy group dropped-out; based on other data and conducted analyses, however, only 10 subjects dropped-out
Selective reporting (reporting bias)	Unclear risk	no protocol available
Other bias	Low risk	no

Tsai 2011

Study characteristics

Methods	**Study design**: randomised (2-arm parallel randomised controlled clinical trial)
	Sample size: 519
	Method of randomisation: no information specified
	Method of concealment: centralised
	Blinding: double-blind (participants, interviewers)
	Analysis: no information specified
	Date the study was conducted: July 2007 - June 2010
Participants	**Location**: Taiwan
	Total N randomised: 92

Tsai 2011 *(Continued)*

Intervention n: 46 (65 % male; age M = 61, SD = 11)

Control n: 46 (63 % male; age M = 65, SD = 11)

Inclusion criteria: first or recurrent Ischaemic stroke (within last 4 weeks); no depression at baseline

Diagnostic criteria - long-term physical condition: stroke is diagnosed by abnormal neurological symptoms based on the participant's statement and imaging

Diagnostic criteria - depression:

- diagnosis according to DSM-IV
- HAM-D modified 17-item version cut-off score ≥ 10 (with item 14 sexual behaviour not rated)

Exclusion criteria: possible concurrent depression (HAM-D ≥ 10); impairment of communication; severe cognitive impairment (MMSE score ≤ 15); use of antidepressants (within 2 weeks of stroke); history of depression, psychosis or severe substance abuse; transit Ischaemic attack

History of depression: no

Interventions	**Intervention**: milnacipran
	- < 1 week: daily dose of 50 mg
	- > 1 week: daily dose titrated up to 100 mg
	Control: matched placebo
	Other treatment: -
	Duration of treatment: 12 months
	Length of follow-up: 12 months (at baseline, 1, 3, 6, 9, and 12 months)
	Other study arms: no
Outcomes	**Primary outcome**:
	- incidence of depression - diagnosis: diagnosis according to DSM-IV made by a psychiatrist
	- adverse events: drop-outs due to adverse events
	Secondary outcome:
	- incidence of depression - cut-off: N/A
	- severity of depression: modified HAM-D-17 (without item 14 sexual behaviour) cut-off score ≥ 10
	- cost-effectiveness: N/A
	- cost-utility: N/A
Notes	**Language:** English
	Funding: ChangGung Medical Research Program (CMRPG 660343 and CMRPG 690491)
	Declaration of interest: None reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...the patients were randomly assigned to two groups" (p.264)
Allocation concealment (selection bias)	Low risk	"the randomisation was carried out by our pharmacy department, which has a professional team in charge of the clinical drug trials in our hospital. They pre-

Tsai 2011 *(Continued)*

		pared the drug with an allocation number for each participant based on their random assignment." (p. 264)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"the placebo was tailor-made, and the appearance and weight (starch inside) were the same as that of the active drug, milnacipran." (p. 264) "all the interviewers were blinded to the patient's medication." (p. 264)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	no information specified
Incomplete outcome data (attrition bias) All outcomes	High risk	**numbers randomised**: milnacipran: n = 46; placebo: n = 46; total: N = 92 **number of drop-outs** at 12 months: milnacipran: n = 21; placebo: n = 15; total: N = 36 **numbers analysed** post-intervention: milnacipran: n = 25; placebo: n = 31; total: N = 56 reasons for drop-out (p. 265) milnacipran: n = 21 drop-outs (among these, 7 due to adverse events) placebo: n = 15 drop-outs (among these, 4 due to adverse events) no further information specified
Selective reporting (reporting bias)	High risk	no protocol available; data on HAM-D, National Institutes of Health Stroke Scale, and Barthel Index was only reported for baseline assessment even though they were "assessed in each of the follow-up visits" (p. 264)
Other bias	Low risk	no

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Almeida 2010	participants with antidepressant treatment at baseline included
Beglinger 2014	incidence of depression was no (primary)outcome
Borrelli 2019	no long-term physical condition
Brody 2005	participants recruited on basis of depressive symptoms
Browne 2013	no long-term physical condition
Burns 2007	participants with antidepressant treatment at baseline included
Couch 1976	incidence of depression was no outcome
Dean 1969	no validated measures
de Jonge 2009	mixed study sample

Study	Reason for exclusion
Hackett 2010	participants with antidepressant treatment at baseline included
Hackett 2013	participants with antidepressant treatment at baseline included
Hood 2018	age criteria not fulfilled (14-18 years)
Karp 2016	indicative/selective prevention
Kong 2007	incidence of depression was not reported
Kredentser 2018	no long-term physical condition
Mossey 1996	participants with antidepressant treatment at baseline included
Niedermaier 2004	no suitable control group
Pitceathly 2009	indicative/selective prevention
Pols 2017	mixed study sample
Read 2020	participants with antidepressant treatment at baseline included
Rovner 2014	no suitable control group
van der Aa 2015	indicative/selective prevention
Yeung 2014	data not accessible
Zhang 2013	no suitable control group

Characteristics of studies awaiting classification *[ordered by study ID]*

ChiCTR-TRC-12003489

Methods	randomised parallel controlled trial
Participants	adults after stroke; target size: 244
Interventions	acupuncture therapy
Outcomes	poststroke depression measured by the Hamilton Depression Rating Scale (HAMD)
Study details	
Publication details	
Stated aim of study	
Notes	The study is led by Sun Jian-Hua (principle investigator) in China. Contacting Wei Zhang revealed that data collection was completed and results are planned to be published late 2018. Sun Jian-Hua was contacted again in March 2020 but we were unable to receive any additional information about the status of the study.

EudraCT-2005-005266-37

Methods	double blinded randomised placebo-controlled trial
Participants	adults after acute middle cerebral artery territory infarction; target size: 60
Interventions	escitalopram 10 mg
Outcomes	primary: incidence of poststroke depression measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) after 180 days following acute middle cerebral artery territory infarction, as well as incidence of dementia measured by the Clinical Dementia Rating Scale (CDR, >0,5) after 180 days following acute middle cerebral artery territory infarction.
Study details	
Publication details	2006-01-04
Stated aim of study	unknown
Notes	Sponsor Name: Central Institute for Mental Health, Mannheim, Div. of Gerontopsychiatry

Guneri 2006

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	no corresponding published study or further data could be found

He 2004

Methods	
Participants	
Interventions	
Outcomes	
Study details	

He 2004 *(Continued)*

Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Li 2004

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Lu 2010

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Sander 2017

Methods	multicenter randomised controlled clinical trial
Participants	adults with chronic back pain; target size: 406

Sander 2017 *(Continued)*

Interventions	internet- and mobile-based intervention (IMI) for the prevention of depression
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	The study is led by Harald Baumeister (principal investigator) in Germany. Contacting Lasse Sander revealed that data collection was completed and results are about to be published. As of now, there were no available data to be included in the review.

van Zyl 2006

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	conference paper; no corresponding published study or further data could be found

Wen 2006

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Xu 2006

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Zhong 2013

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Zhou 2008

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	

Zhou 2008 *(Continued)*

Stated aim of study	
Notes	full texts were not accessible, no further information were available

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Zhu 2014

Methods	
Participants	
Interventions	
Outcomes	
Study details	
Publication details	
Stated aim of study	
Notes	full texts were not accessible, no further information were available

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12616000886482

Study name	Randomised trial aiming to prevent development of depression and improve quality of life in individuals with dementia (Alzheimer's disease) through a novel Cognitive Bias Modification intervention
Methods	blinded randomised controlled trial
Participants	target size: 300
Interventions	cognitive bias modification (CBM)
Outcomes	primary: Incidence of clinically significant depressive symptoms in adults with Alzheimer's disease measured by the Cornell Scale for Depression in Dementia (CSDD).
Starting date	2016-07-06
Contact information	andrew.ford@uwa.edu.au; varsha,hirani@uwa.edu.au
Notes	This study is led by Dr. Andrew Ford (principal investigator) in Australia (ACTRN12616000886482). Dr. Ford was contacted in March 2020: the trial is still ongoing.

Madsen 2017

Study name	The effect of MElatonin on Depressive symptoms, Anxiety, CIrcadian and Sleep disturbances in patients after acute coronary syndrome (MEDACIS): study protocol for a randomised controlled trial
Methods	multicenter, double-blinded, placebo-controlled, randomised clinical trial
Participants	target size: 240
Interventions	25 mg exogenous melatonin
Outcomes	primary: Incidence of clinically significant depressive symptoms measured by the Major Depression Inventory (MDI)
Starting date	2015
Contact information	michael_madsen88@hotmail.com
Notes	The study is led by Dr. Michael Tvilling Madsen (principal investigator) in Denmark (NCT02451293). Dr. Madsen was contacted again in March 2020 but we were unable to receive any additional information about the status of the study.

DATA AND ANALYSES

Comparison 1. Psychological intervention versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Incidence of depression (diagnosis) - post-intervention	1	194	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.20, 0.95]
1.2 Incidence of depression (diagnosis) - short-term	1	190	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.36, 1.38]
1.3 Dropouts due to any cause - post-intervention	1	206	Odds Ratio (M-H, Random, 95% CI)	5.21 [1.11, 24.40]
1.4 Dropouts due to any cause - short-term	1	206	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.58, 4.77]

Analysis 1.1. Comparison 1: Psychological intervention versus usual care, Outcome 1: Incidence of depression (diagnosis) - post-intervention

Study or Subgroup	psychological Events	Total	TAU Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Rovner 2007	11	95	23	99	100.0%	0.43 [0.20 , 0.95]	
Total (95% CI)		**95**		**99**	**100.0%**	**0.43 [0.20 , 0.95]**	
Total events:	11		23				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours psychological   Favours TAU
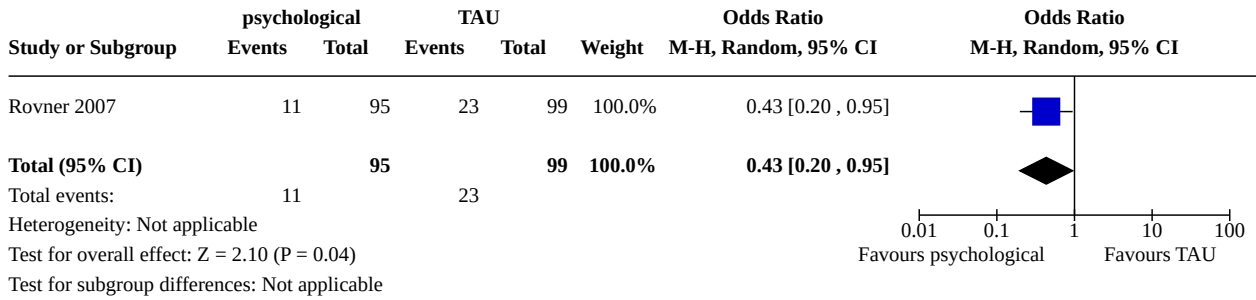
Analysis 1.2. Comparison 1: Psychological intervention versus usual care, Outcome 2: Incidence of depression (diagnosis) - short-term

Study or Subgroup	psychological Events	Total	TAU Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Rovner 2007	20	95	26	95	100.0%	0.71 [0.36 , 1.38]	
Total (95% CI)		**95**		**95**	**100.0%**	**0.71 [0.36 , 1.38]**	
Total events:	20		26				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours psychological   Favours TAU
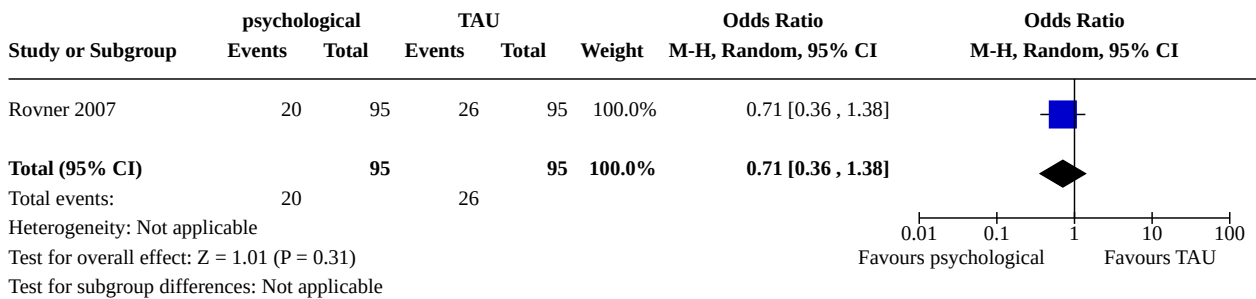
Analysis 1.3. Comparison 1: Psychological intervention versus usual care, Outcome 3: Dropouts due to any cause - post-intervention

Study or Subgroup	psychological Events	Total	TAU Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Rovner 2007	10	105	2	101	100.0%	5.21 [1.11 , 24.40]	
Total (95% CI)		**105**		**101**	**100.0%**	**5.21 [1.11 , 24.40]**	
Total events:	10		2				

Heterogeneity: Not applicable
Test for overall effect: Z = 2.10 (P = 0.04)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours psychological   Favours TAU
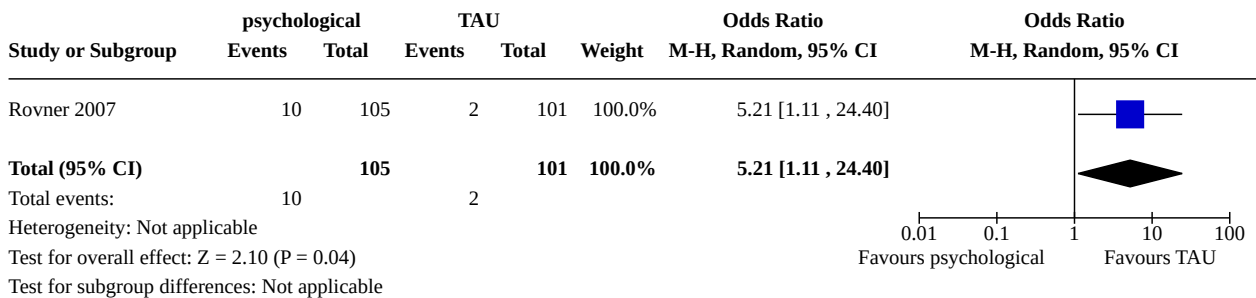
Analysis 1.4. Comparison 1: Psychological intervention versus usual care, Outcome 4: Dropouts due to any cause - short-term

Study or Subgroup	psychological		TAU		Weight	Odds Ratio	Odds Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI
Rovner 2007	10	105	6	101	100.0%	1.67 [0.58 , 4.77]	
Total (95% CI)		**105**		**101**	**100.0%**	**1.67 [0.58 , 4.77]**	
Total events:	10		6				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.95 (P = 0.34)

Test for subgroup differences: Not applicable
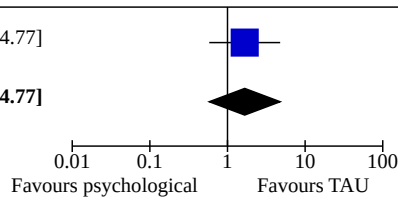
0.01 0.1 1 10 100
Favours psychological Favours TAU

Comparison 2. Pharmacological intervention versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Incidence of depression (all) - post-intervention	9	814	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.20, 0.49]
2.2 Incidence of depression (all) - medium-term	3	233	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.23, 2.82]
2.3 Incidence of depression (diagnosis) - post-intervention	5	474	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.52]
2.4 Incidence of depression (diagnosis) - short-term	1	23	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.08, 2.46]
2.5 Incidence of depression (diagnosis) - medium-term	2	139	Odds Ratio (M-H, Random, 95% CI)	1.50 [0.06, 39.71]
2.6 Acceptability - dropouts due to adverse events	5	561	Odds Ratio (M-H, Random, 95% CI)	2.05 [1.07, 3.89]
2.7 Acceptability - dropouts due to any cause - post-intervention	9	962	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.73, 1.73]
2.8 Acceptability - dropouts due to any cause - medium-term	3	327	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.69, 1.86]
2.9 Incidence of depression (cut-off) - post-intervention	3	241	Odds Ratio (M-H, Random, 95% CI)	0.26 [0.13, 0.51]
2.10 Incidence of depression (diagnosis or cut-off) - post-intervention	1	99	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.26, 2.00]
2.11 Incidence of depression (diagnosis or cut-off) - medium-term	1	94	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.27, 1.74]
2.12 Severity of depression - post-intervention	2	163	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.91, 0.54]
2.13 Severity of depression - short-term	1	87	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.75, 0.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.14 Severity of depression - medium-term	2	139	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.72, 1.09]

Analysis 2.1. Comparison 2: Pharmacological intervention versus placebo, Outcome 1: Incidence of depression (all) - post-intervention

	pharmacological		placebo			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Almeida 2006	8	48	11	51	19.3%	0.73 [0.26 , 2.00]	
Hansen 2012	2	85	10	89	8.2%	0.19 [0.04 , 0.90]	
Hansen 2014	3	27	9	16	8.2%	0.10 [0.02 , 0.46]	
Lydiatt 2013	6	36	16	44	17.2%	0.35 [0.12 , 1.02]	
Narushima 2002	4	28	5	15	8.7%	0.33 [0.07 , 1.51]	
Novack 2009	0	48	3	48	2.2%	0.13 [0.01 , 2.67]	
Rasmussen 2003	5	61	13	57	16.2%	0.30 [0.10 , 0.91]	
Robinson 2008	5	52	13	53	15.9%	0.33 [0.11 , 1.00]	
Tsai 2011	1	25	7	31	4.2%	0.14 [0.02 , 1.25]	
Total (95% CI)		**410**		**404**	**100.0%**	**0.31 [0.20 , 0.49]**	
Total events:	34		87				

Heterogeneity: Tau² = 0.00; Chi² = 6.13, df = 8 (P = 0.63); I² = 0%

Test for overall effect: Z = 5.12 (P < 0.00001)

Test for subgroup differences: Not applicable

Favours pharmacological 0.01 0.1 1 10 100 Favours placebo

Analysis 2.2. Comparison 2: Pharmacological intervention versus placebo, Outcome 2: Incidence of depression (all) - medium-term

	pharmacological		placebo			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Almeida 2006	10	44	15	50	49.9%	0.69 [0.27 , 1.74]	
Novack 2009	3	36	7	36	36.0%	0.38 [0.09 , 1.59]	
Robinson 2008	4	34	0	33	14.2%	9.89 [0.51 , 191.27]	
Total (95% CI)		**114**		**119**	**100.0%**	**0.81 [0.23 , 2.82]**	
Total events:	17		22				

Heterogeneity: Tau² = 0.59; Chi² = 3.93, df = 2 (P = 0.14); I² = 49%

Test for overall effect: Z = 0.34 (P = 0.74)

Test for subgroup differences: Not applicable

Favours pharmacological 0.01 0.1 1 10 100 Favours placebo

Analysis 2.3. Comparison 2: Pharmacological intervention versus placebo, Outcome 3: Incidence of depression (diagnosis) - post-intervention

Study or Subgroup	pharmacological Events	pharmacological Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Hansen 2012	2	85	10	89	21.0%	0.19 [0.04 , 0.90]	
Narushima 2002	4	28	5	15	22.2%	0.33 [0.07 , 1.51]	
Novack 2009	0	48	3	48	5.6%	0.13 [0.01 , 2.67]	
Robinson 2008	5	52	13	53	40.6%	0.33 [0.11 , 1.00]	
Tsai 2011	1	25	7	31	10.7%	0.14 [0.02 , 1.25]	
Total (95% CI)		**238**		**236**	**100.0%**	**0.26 [0.13 , 0.52]**	
Total events:	12		38				

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)
Test for subgroup differences: Not applicable

Favours pharmacological Favours placebo

Analysis 2.4. Comparison 2: Pharmacological intervention versus placebo, Outcome 4: Incidence of depression (diagnosis) - short-term

Study or Subgroup	pharmacological Events	pharmacological Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Lydiatt 2008	4	13	5	10	100.0%	0.44 [0.08 , 2.46]	
Total (95% CI)		**13**		**10**	**100.0%**	**0.44 [0.08 , 2.46]**	
Total events:	4		5				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

Favours pharmacological Favours placebo

Analysis 2.5. Comparison 2: Pharmacological intervention versus placebo, Outcome 5: Incidence of depression (diagnosis) - medium-term

Study or Subgroup	pharmacological Events	pharmacological Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Novack 2009	3	36	7	36	57.6%	0.38 [0.09 , 1.59]	
Robinson 2008	4	34	0	33	42.4%	9.89 [0.51 , 191.27]	
Total (95% CI)		**70**		**69**	**100.0%**	**1.50 [0.06 , 39.71]**	
Total events:	7		7				

Heterogeneity: Tau² = 4.30; Chi² = 4.04, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable

Favours pharmacological Favours placebo

Analysis 2.6. Comparison 2: Pharmacological intervention versus placebo, Outcome 6: Acceptability - dropouts due to adverse events

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Hansen 2012	8	120	5	119	31.4%	1.63 [0.52 , 5.13]	
Hansen 2014	0	28	2	26	4.4%	0.17 [0.01 , 3.76]	
Lydiatt 2008	2	15	0	13	4.2%	5.00 [0.22 , 114.22]	
Lydiatt 2013	14	74	5	74	35.6%	3.22 [1.10 , 9.46]	
Tsai 2011	7	46	4	46	24.4%	1.88 [0.51 , 6.94]	
Total (95% CI)		**283**		**278**	**100.0%**	**2.05 [1.07 , 3.89]**	
Total events:	31		16				

Heterogeneity: Tau² = 0.00; Chi² = 3.65, df = 4 (P = 0.46); I² = 0%

Test for overall effect: Z = 2.18 (P = 0.03)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours pharmacological   Favours placebo

Analysis 2.7. Comparison 2: Pharmacological intervention versus placebo, Outcome 7: Acceptability - dropouts due to any cause - post-intervention

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Hansen 2012	35	120	30	119	24.7%	1.22 [0.69 , 2.16]	
Hansen 2014	1	28	10	26	3.7%	0.06 [0.01 , 0.51]	
Lydiatt 2008	2	15	3	13	4.3%	0.51 [0.07 , 3.68]	
Lydiatt 2013	38	74	30	74	21.8%	1.55 [0.81 , 2.97]	
Narushima 2002	4	32	1	16	3.3%	2.14 [0.22 , 20.93]	
Novack 2009	1	49	2	50	2.9%	0.50 [0.04 , 5.70]	
Rasmussen 2003	9	70	10	67	13.5%	0.84 [0.32 , 2.22]	
Robinson 2008	7	59	5	58	9.8%	1.43 [0.43 , 4.78]	
Tsai 2011	21	46	15	46	16.2%	1.74 [0.74 , 4.05]	
Total (95% CI)		**493**		**469**	**100.0%**	**1.13 [0.73 , 1.73]**	
Total events:	118		106				

Heterogeneity: Tau² = 0.11; Chi² = 11.10, df = 8 (P = 0.20); I² = 28%

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours pharmacological   Favours placebo

Analysis 2.8. Comparison 2: Pharmacological intervention versus placebo, Outcome 8: Acceptability - dropouts due to any cause - medium-term

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Almeida 2006	11	55	6	56	21.6%	2.08 [0.71 , 6.10]	
Novack 2009	13	49	14	50	31.9%	0.93 [0.38 , 2.25]	
Robinson 2008	25	59	25	58	46.5%	0.97 [0.47 , 2.02]	
Total (95% CI)		**163**		**164**	**100.0%**	**1.13 [0.69 , 1.86]**	
Total events:	49		45				

Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours pharmacological   Favours placebo

Analysis 2.9. Comparison 2: Pharmacological intervention versus placebo, Outcome 9: Incidence of depression (cut-off) - post-intervention

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Hansen 2014	3	27	9	16	19.6%	0.10 [0.02 , 0.46]	
Lydiatt 2013	6	36	16	44	41.4%	0.35 [0.12 , 1.02]	
Rasmussen 2003	5	61	13	57	38.9%	0.30 [0.10 , 0.91]	
Total (95% CI)		**124**		**117**	**100.0%**	**0.26 [0.13 , 0.51]**	
Total events:	14		38				

Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 2 (P = 0.39); I² = 0%
Test for overall effect: Z = 3.86 (P = 0.0001)
Test for subgroup differences: Not applicable

Favours pharmacological   Favours placebo

Analysis 2.10. Comparison 2: Pharmacological intervention versus placebo, Outcome 10: Incidence of depression (diagnosis or cut-off) - post-intervention

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Almeida 2006	8	48	11	51	100.0%	0.73 [0.26 , 2.00]	
Total (95% CI)		**48**		**51**	**100.0%**	**0.73 [0.26 , 2.00]**	
Total events:	8		11				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable

Favours pharmacological   Favours placebo
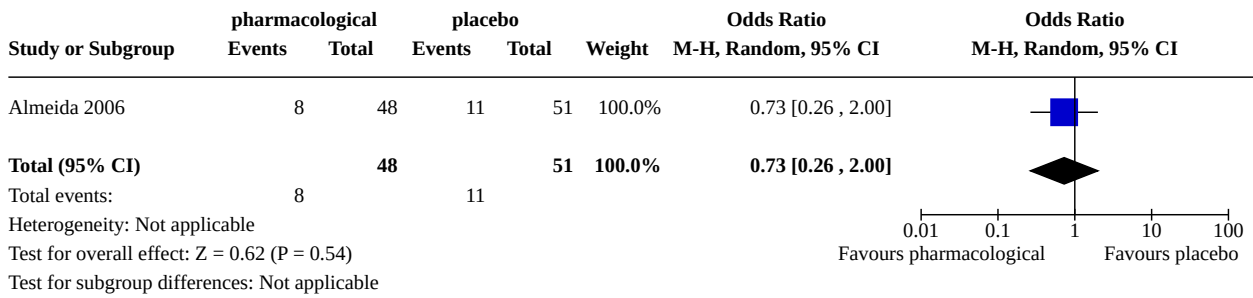
Analysis 2.11. Comparison 2: Pharmacological intervention versus placebo, Outcome 11: Incidence of depression (diagnosis or cut-off) - medium-term

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Almeida 2006	10	44	15	50	100.0%	0.69 [0.27 , 1.74]	
Total (95% CI)		**44**		**50**	**100.0%**	**0.69 [0.27 , 1.74]**	
Total events:	10		15				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable

Favours pharmacological   Favours placebo
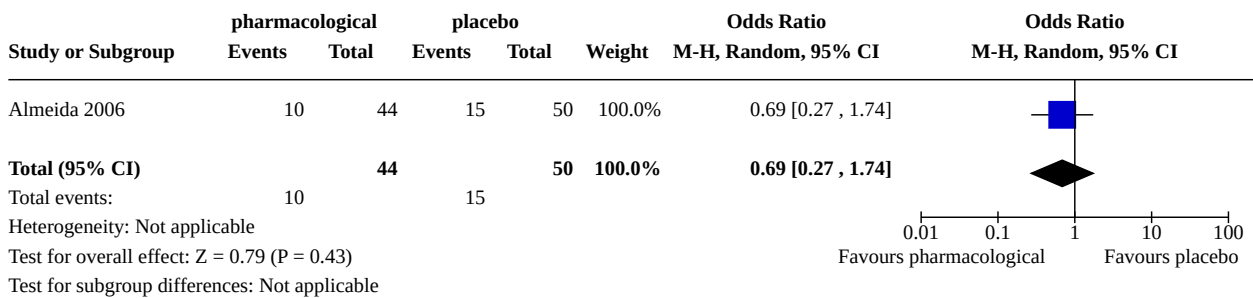
Analysis 2.12. Comparison 2: Pharmacological intervention versus placebo, Outcome 12: Severity of depression - post-intervention

Study or Subgroup	pharmacological Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
Novack 2009	89	11.4	48	96	14	48	51.5%	-0.54 [-0.95 , -0.14]	
Robinson 2008	5.6	3.3	34	5	2.8	33	48.5%	0.19 [-0.29 , 0.67]	
Total (95% CI)			82			81	100.0%	-0.19 [-0.91 , 0.54]	

Heterogeneity: Tau² = 0.22; Chi² = 5.27, df = 1 (P = 0.02); I² = 81%
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable

-100   -50   0   50   100
Favours pharmacological   Favours placebo

Analysis 2.13. Comparison 2: Pharmacological intervention versus placebo, Outcome 13: Severity of depression - short-term

Study or Subgroup	pharmacological Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
Novack 2009	87.2	12.4	41	91.5	13.3	46	100.0%	-0.33 [-0.75 , 0.09]	
Total (95% CI)			41			46	100.0%	-0.33 [-0.75 , 0.09]	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable

-100   -50   0   50   100
Favours pharmacological   Favours placebo

Analysis 2.14. Comparison 2: Pharmacological intervention versus placebo, Outcome 14: Severity of depression - medium-term
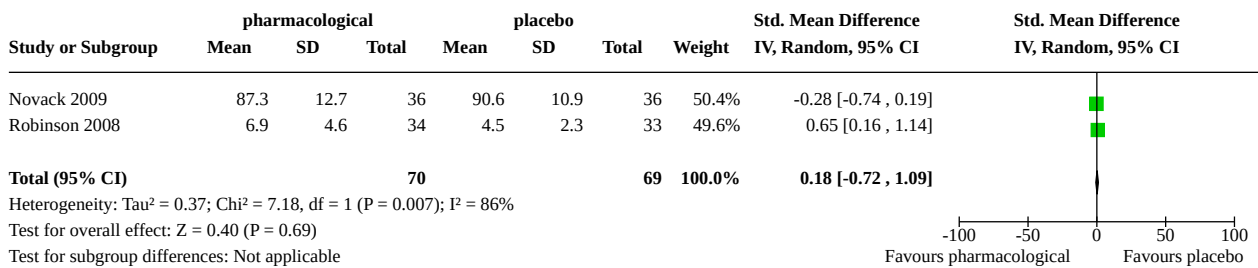
Study or Subgroup	pharmacological Mean	SD	Total	placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Std. Mean Difference IV, Random, 95% CI
Novack 2009	87.3	12.7	36	90.6	10.9	36	50.4%	-0.28 [-0.74 , 0.19]	
Robinson 2008	6.9	4.6	34	4.5	2.3	33	49.6%	0.65 [0.16 , 1.14]	
Total (95% CI)			70			69	100.0%	0.18 [-0.72 , 1.09]	

Heterogeneity: Tau² = 0.37; Chi² = 7.18, df = 1 (P = 0.007); I² = 86%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable

-100   -50   0   50   100
Favours pharmacological   Favours placebo

Comparison 3. Sensitivity analyses on quality of studies - impact of missing data (best & worst case scenarios) - incidence of depression: psychological intervention versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 best case scenario	1	412	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.27, 0.72]
3.1.1 post-intervention	1	206	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.16, 0.77]
3.1.2 short-term	1	206	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.27, 0.96]
3.2 worst case scenario	1	412	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.64, 1.57]
3.2.1 post-intervention	1	206	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.44, 1.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.2 short-term	1	206	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.62, 2.13]

Analysis 3.1. Comparison 3: Sensitivity analyses on quality of studies - impact of missing data (best & worst case scenarios) - incidence of depression: psychological intervention versus placebo, Outcome 1: best case scenario

Study or Subgroup	psychological Events	Total	TAU Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
3.1.1 post-intervention							
Rovner 2007	11	105	25	101	41.0%	0.36 [0.16 , 0.77]	
Subtotal (95% CI)		**105**		**101**	**41.0%**	**0.36 [0.16 , 0.77]**	
Total events:	11		25				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.63 (P = 0.009)							
3.1.2 short-term							
Rovner 2007	20	105	32	101	59.0%	0.51 [0.27 , 0.96]	
Subtotal (95% CI)		**105**		**101**	**59.0%**	**0.51 [0.27 , 0.96]**	
Total events:	20		32				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.07 (P = 0.04)							
Total (95% CI)		**210**		**202**	**100.0%**	**0.44 [0.27 , 0.72]**	
Total events:	31		57				

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%

Test for overall effect: Z = 3.27 (P = 0.001)

Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%

0.01   0.1   1   10   100
Favours [psychological]   Favours [TAU]

Analysis 3.2. Comparison 3: Sensitivity analyses on quality of studies - impact of missing data (best & worst case scenarios) - incidence of depression: psychological intervention versus placebo, Outcome 2: worst case scenario

Study or Subgroup	psychological Events	Total	TAU Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
3.2.1 post-intervention							
Rovner 2007	21	105	23	101	45.9%	0.85 [0.44 , 1.65]	
Subtotal (95% CI)		**105**		**101**	**45.9%**	**0.85 [0.44 , 1.65]**	
Total events:	21		23				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.49 (P = 0.63)							
3.2.2 short-term							
Rovner 2007	30	105	26	101	54.1%	1.15 [0.62 , 2.13]	
Subtotal (95% CI)		**105**		**101**	**54.1%**	**1.15 [0.62 , 2.13]**	
Total events:	30		26				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							
Total (95% CI)		**210**		**202**	**100.0%**	**1.00 [0.64 , 1.57]**	
Total events:	51		49				
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%							
Test for overall effect: Z = 0.01 (P = 0.99)							
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%							

0.01 0.1 1 10 100
Favours [psychological]   Favours [TAU]
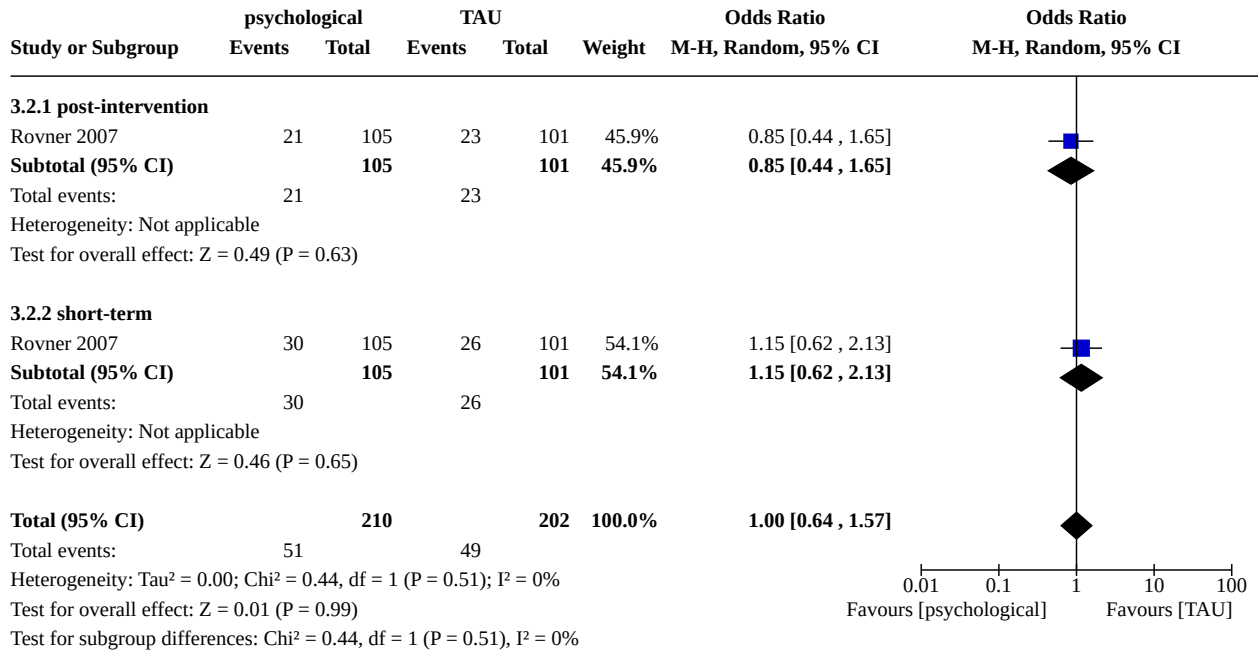
Comparison 4. Sensitivity analyses on quality of studies - failing to double-blind - incidence of depression: pharmacological intervention versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 post-intervention	4	431	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.11, 0.53]
4.1.1 diagnosis	4	431	Odds Ratio (M-H, Random, 95% CI)	0.24 [0.11, 0.53]

Analysis 4.1. Comparison 4: Sensitivity analyses on quality of studies - failing to double-blind - incidence of depression: pharmacological intervention versus placebo, Outcome 1: post-intervention

Study or Subgroup	pharmacological Events	pharmacological Total	placebo Events	placebo Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
4.1.1 diagnosis							
Hansen 2012	2	85	10	89	26.9%	0.19 [0.04 , 0.90]	
Novack 2009	0	48	3	48	7.2%	0.13 [0.01 , 2.67]	
Robinson 2008	5	52	13	53	52.1%	0.33 [0.11 , 1.00]	
Tsai 2011	1	25	7	31	13.7%	0.14 [0.02 , 1.25]	
Subtotal (95% CI)		210		221	100.0%	**0.24 [0.11 , 0.53]**	
Total events:	8		33				

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0004)

Total (95% CI)		210		221	100.0%	**0.24 [0.11 , 0.53]**	
Total events:	8		33				

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0004)
Test for subgroup differences: Not applicable

0.01 0.1 1 10 100
Favours [pharmacological]   Favours [placebo]
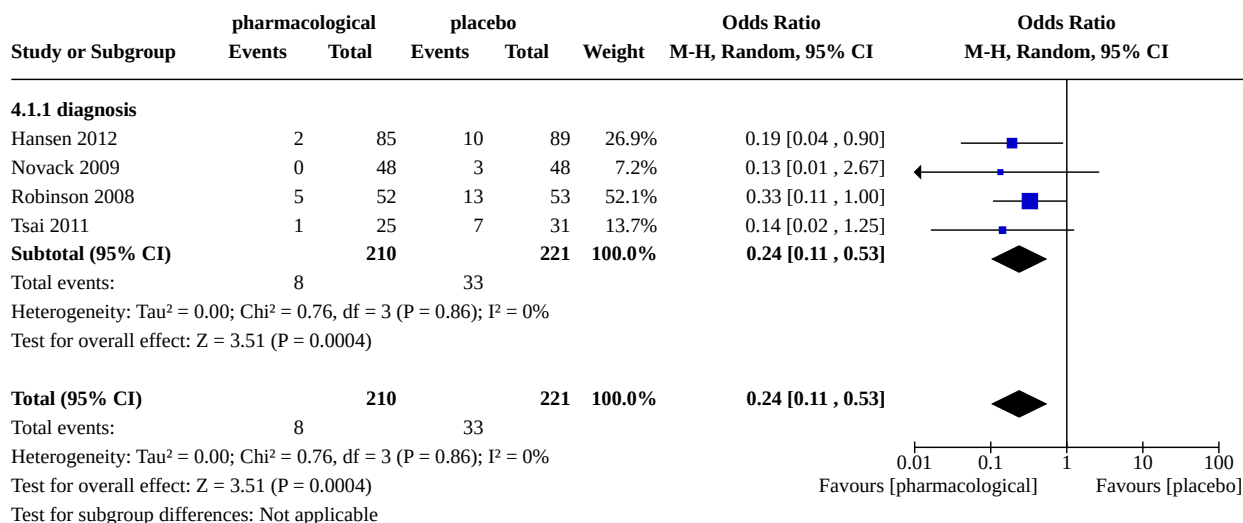
Comparison 5. Sensitivity analyses on quality of studies - impact of missing data (best & worst case scenarios) - incidence of depression: pharmacological intervention versus placebo

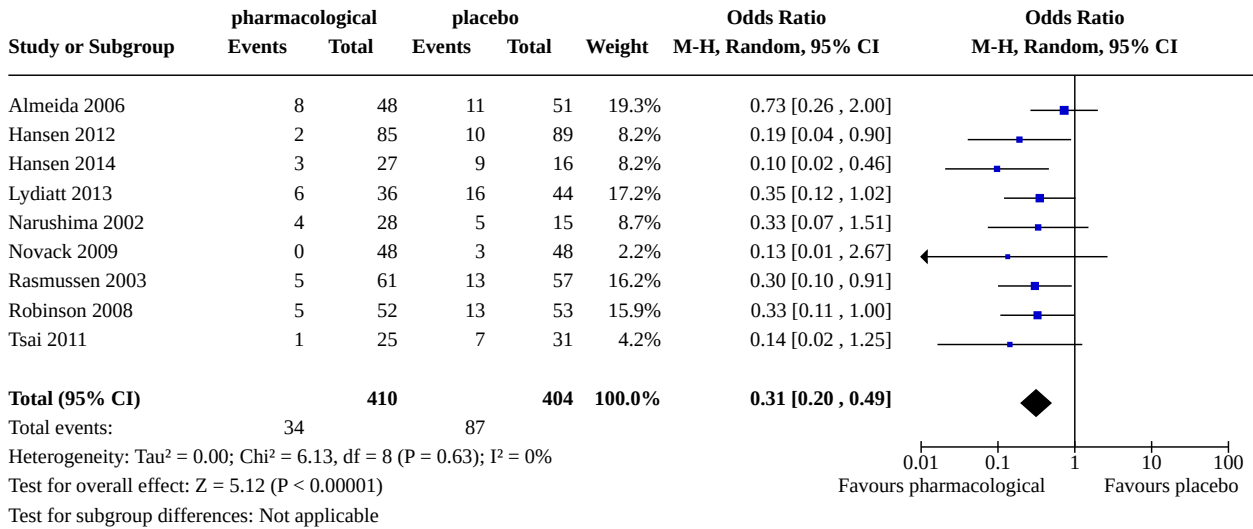| Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 best case scenario	10	1400	Odds Ratio (M-H, Random, 95% CI)	0.15 [0.09, 0.24]
5.1.1 post-intervention	9	1045	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.07, 0.24]
5.1.2 short-term	1	28	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.51]
5.1.3 medium-term	3	327	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.06, 0.43]
5.2 worst case scenario	10	1400	Odds Ratio (M-H, Random, 95% CI)	1.63 [0.97, 2.73]
5.2.1 post-intervention	9	1045	Odds Ratio (M-H, Random, 95% CI)	1.35 [0.74, 2.44]
5.2.2 short-term	1	28	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.23, 4.89]
5.2.3 medium-term	3	327	Odds Ratio (M-H, Random, 95% CI)	4.81 [0.92, 25.29]

Analysis 5.1. Comparison 5: Sensitivity analyses on quality of studies - impact of missing data (best & worst case scenarios) - incidence of depression: pharmacological intervention versus placebo, Outcome 1: best case scenario

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
5.1.1 post-intervention							
Almeida 2006	8	55	16	56	10.5%	0.43 [0.16 , 1.10]	
Hansen 2012	2	120	40	119	6.7%	0.03 [0.01 , 0.14]	
Hansen 2014	3	28	19	26	6.6%	0.04 [0.01 , 0.19]	
Lydiatt 2013	6	74	25	74	10.4%	0.17 [0.07 , 0.45]	
Narushima 2002	4	32	6	16	6.7%	0.24 [0.06 , 1.02]	
Novack 2009	0	49	5	50	2.3%	0.08 [0.00 , 1.55]	
Rasmussen 2003	5	70	23	67	9.7%	0.15 [0.05 , 0.42]	
Robinson 2008	5	59	18	58	9.4%	0.21 [0.07 , 0.60]	
Tsai 2011	1	46	22	46	4.1%	0.02 [0.00 , 0.19]	
Subtotal (95% CI)		**533**		**512**	**66.3%**	**0.13 [0.07 , 0.24]**	
Total events:	34		174				
Heterogeneity: Tau² = 0.42; Chi² = 15.97, df = 8 (P = 0.04); I² = 50%							
Test for overall effect: Z = 6.46 (P < 0.00001)							
5.1.2 short-term							
Lydiatt 2008	4	15	7	13	6.0%	0.31 [0.06 , 1.51]	
Subtotal (95% CI)		**15**		**13**	**6.0%**	**0.31 [0.06 , 1.51]**	
Total events:	4		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.45 (P = 0.15)							
5.1.3 medium-term							
Almeida 2006	10	55	21	56	11.2%	0.37 [0.15 , 0.89]	
Novack 2009	3	49	21	50	7.7%	0.09 [0.02 , 0.33]	
Robinson 2008	4	59	25	58	8.8%	0.10 [0.03 , 0.30]	
Subtotal (95% CI)		**163**		**164**	**27.7%**	**0.16 [0.06 , 0.43]**	
Total events:	17		67				
Heterogeneity: Tau² = 0.45; Chi² = 4.93, df = 2 (P = 0.09); I² = 59%							
Test for overall effect: Z = 3.63 (P = 0.0003)							
Total (95% CI)		**711**		**689**	**100.0%**	**0.15 [0.09 , 0.24]**	
Total events:	55		248				
Heterogeneity: Tau² = 0.32; Chi² = 21.85, df = 12 (P = 0.04); I² = 45%							
Test for overall effect: Z = 7.93 (P < 0.00001)							
Test for subgroup differences: Chi² = 1.06, df = 2 (P = 0.59), I² = 0%							

0.01   0.1   1   10   100
Favours [pharmacological]   Favours [placebo]

Analysis 5.2. Comparison 5: Sensitivity analyses on quality of studies - impact of missing data (best & worst case scenarios) - incidence of depression: pharmacological intervention versus placebo, Outcome 2: worst case scenario

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
5.2.1 post-intervention							
Almeida 2006	15	55	11	56	9.1%	1.53 [0.63 , 3.72]	
Hansen 2012	37	120	10	119	9.9%	4.86 [2.28 , 10.33]	
Hansen 2014	4	28	9	26	6.8%	0.31 [0.08 , 1.19]	
Lydiatt 2013	20	74	16	74	9.9%	1.34 [0.63 , 2.86]	
Narushima 2002	8	32	5	16	6.9%	0.73 [0.19 , 2.76]	
Novack 2009	1	49	3	50	3.6%	0.33 [0.03 , 3.25]	
Rasmussen 2003	14	70	13	67	9.4%	1.04 [0.45 , 2.41]	
Robinson 2008	12	59	13	58	9.1%	0.88 [0.36 , 2.14]	
Tsai 2011	22	46	7	46	8.6%	5.11 [1.90 , 13.76]	
Subtotal (95% CI)		**533**		**512**	**73.2%**	**1.35 [0.74 , 2.44]**	
Total events:	133		87				
Heterogeneity: Tau² = 0.54; Chi² = 25.45, df = 8 (P = 0.001); I² = 69%							
Test for overall effect: Z = 0.98 (P = 0.33)							
5.2.2 short-term							
Lydiatt 2008	6	15	5	13	6.0%	1.07 [0.23 , 4.89]	
Subtotal (95% CI)		**15**		**13**	**6.0%**	**1.07 [0.23 , 4.89]**	
Total events:	6		5				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.08 (P = 0.93)							
5.2.3 medium-term							
Almeida 2006	21	55	15	56	9.6%	1.69 [0.76 , 3.77]	
Novack 2009	16	49	7	50	8.5%	2.98 [1.10 , 8.07]	
Robinson 2008	29	59	0	58	2.6%	113.16 [6.68 , 1916.21]	
Subtotal (95% CI)		**163**		**164**	**20.8%**	**4.81 [0.92 , 25.29]**	
Total events:	66		22				
Heterogeneity: Tau² = 1.57; Chi² = 10.46, df = 2 (P = 0.005); I² = 81%							
Test for overall effect: Z = 1.86 (P = 0.06)							
Total (95% CI)		**711**		**689**	**100.0%**	**1.63 [0.97 , 2.73]**	
Total events:	205		114				
Heterogeneity: Tau² = 0.56; Chi² = 37.06, df = 12 (P = 0.0002); I² = 68%							
Test for overall effect: Z = 1.84 (P = 0.07)							
Test for subgroup differences: Chi² = 2.21, df = 2 (P = 0.33), I² = 9.7%							

0.01 0.1 1 10 100
Favours [pharmacological]   Favours [placebo]

Comparison 6. Sensitivity analyses on length of treatment - post-randomisation - incidence of depression: pharmacological intervention versus placebo

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
6.1 short-term	6	384	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.21, 0.64]
6.1.1 diagnosis	3	162	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.12, 0.96]
6.1.2 cut-off	2	123	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.06, 0.72]
6.1.3 diagnosis OR cut-off	1	99	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.26, 2.00]

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
6.2 medium-term	6	619	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.22, 0.61]
6.2.1 diagnosis	4	407	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.13, 0.57]
6.2.2 cut-off	1	118	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.10, 0.91]
6.2.3 diagnosis OR cut-off	1	94	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.27, 1.74]
6.3 long-term	1	67	Odds Ratio (M-H, Random, 95% CI)	9.89 [0.51, 191.27]
6.3.1 diagnosis	1	67	Odds Ratio (M-H, Random, 95% CI)	9.89 [0.51, 191.27]

Analysis 6.1. Comparison 6: Sensitivity analyses on length of treatment - post-randomisation - incidence of depression: pharmacological intervention versus placebo, Outcome 1: short-term

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
6.1.1 diagnosis							
Lydiatt 2008	4	13	5	10	10.9%	0.44 [0.08 , 2.46]	
Narushima 2002	4	28	5	15	14.0%	0.33 [0.07 , 1.51]	
Novack 2009	0	48	3	48	3.6%	0.13 [0.01 , 2.67]	
Subtotal (95% CI)		**89**		**73**	**28.6%**	**0.33 [0.12 , 0.96]**	
Total events:	8		13				
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%							
Test for overall effect: Z = 2.04 (P = 0.04)							
6.1.2 cut-off							
Hansen 2014	3	27	9	16	13.2%	0.10 [0.02 , 0.46]	
Lydiatt 2013	6	36	16	44	27.5%	0.35 [0.12 , 1.02]	
Subtotal (95% CI)		**63**		**60**	**40.7%**	**0.21 [0.06 , 0.72]**	
Total events:	9		25				
Heterogeneity: Tau² = 0.36; Chi² = 1.77, df = 1 (P = 0.18); I² = 44%							
Test for overall effect: Z = 2.49 (P = 0.01)							
6.1.3 diagnosis OR cut-off							
Almeida 2006	8	48	11	51	30.7%	0.73 [0.26 , 2.00]	
Subtotal (95% CI)		**48**		**51**	**30.7%**	**0.73 [0.26 , 2.00]**	
Total events:	8		11				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.62 (P = 0.54)							
Total (95% CI)		**200**		**184**	**100.0%**	**0.36 [0.21 , 0.64]**	
Total events:	25		49				
Heterogeneity: Tau² = 0.01; Chi² = 5.08, df = 5 (P = 0.41); I² = 2%							
Test for overall effect: Z = 3.48 (P = 0.0005)							
Test for subgroup differences: Chi² = 2.52, df = 2 (P = 0.28), I² = 20.6%							

0.01 0.1 1 10 100
Favours [pharmacological]   Favours [placebo]

Analysis 6.2. Comparison 6: Sensitivity analyses on length of treatment - post-randomisation - incidence of depression: pharmacological intervention versus placebo, Outcome 2: medium-term

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
6.2.1 diagnosis							
Hansen 2012	2	85	10	89	10.7%	0.19 [0.04 , 0.90]	
Novack 2009	3	36	7	36	12.4%	0.38 [0.09 , 1.59]	
Robinson 2008	5	52	13	53	20.7%	0.33 [0.11 , 1.00]	
Tsai 2011	1	25	7	31	5.5%	0.14 [0.02 , 1.25]	
Subtotal (95% CI)		**198**		**209**	**49.2%**	**0.27 [0.13 , 0.57]**	
Total events:	11		37				
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%							
Test for overall effect: Z = 3.50 (P = 0.0005)							
6.2.2 cut-off							
Rasmussen 2003	5	61	13	57	21.1%	0.30 [0.10 , 0.91]	
Subtotal (95% CI)		**61**		**57**	**21.1%**	**0.30 [0.10 , 0.91]**	
Total events:	5		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.12 (P = 0.03)							
6.2.3 diagnosis OR cut-off							
Almeida 2006	10	44	15	50	29.8%	0.69 [0.27 , 1.74]	
Subtotal (95% CI)		**44**		**50**	**29.8%**	**0.69 [0.27 , 1.74]**	
Total events:	10		15				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							
Total (95% CI)		**303**		**316**	**100.0%**	**0.37 [0.22 , 0.61]**	
Total events:	26		65				
Heterogeneity: Tau² = 0.00; Chi² = 3.34, df = 5 (P = 0.65); I² = 0%							
Test for overall effect: Z = 3.86 (P = 0.0001)							
Test for subgroup differences: Chi² = 2.48, df = 2 (P = 0.29), I² = 19.3%							

0.01 0.1 1 10 100
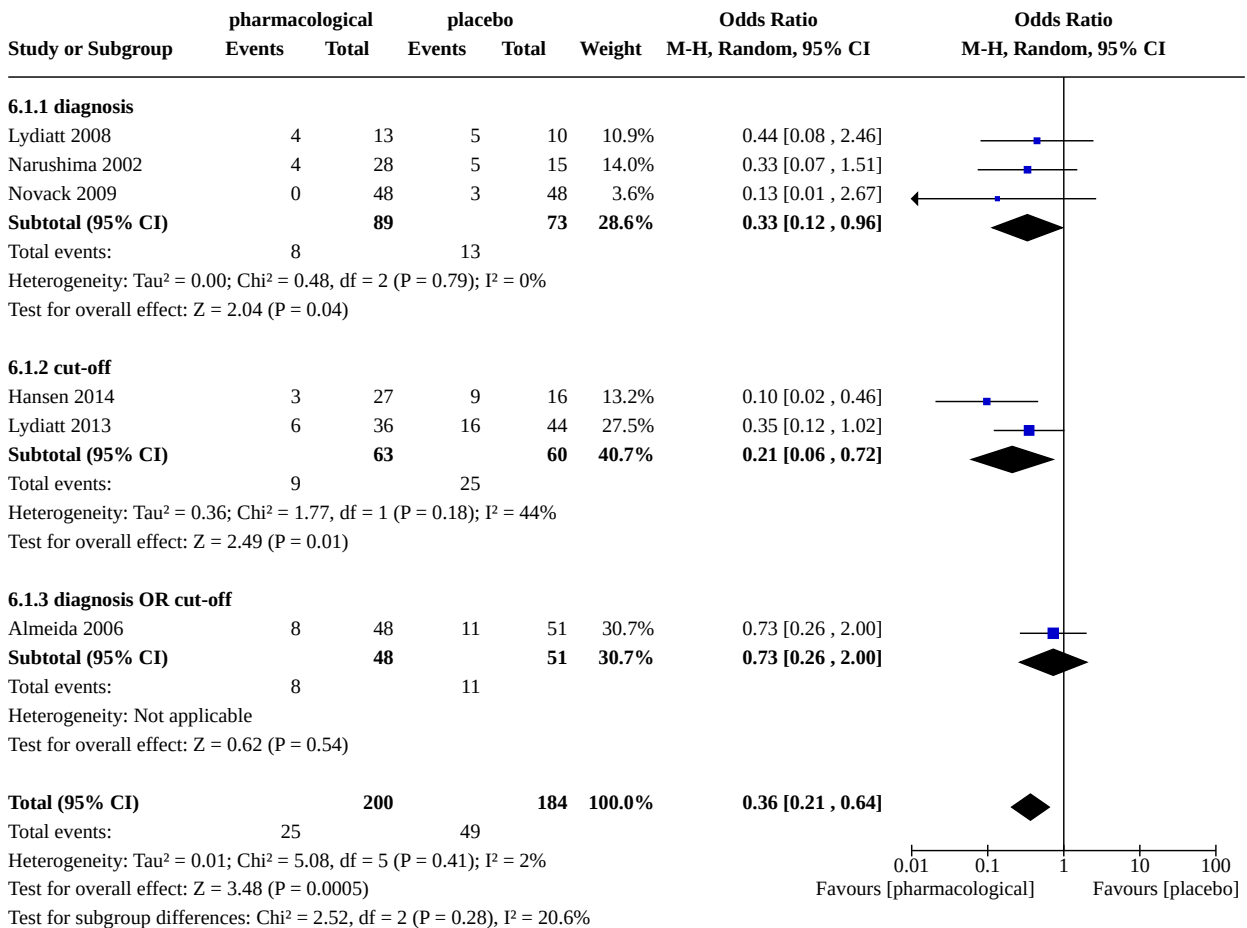Favours [pharmacological]   Favours [placebo]

Analysis 6.3. Comparison 6: Sensitivity analyses on length of treatment - post-randomisation - incidence of depression: pharmacological intervention versus placebo, Outcome 3: long-term
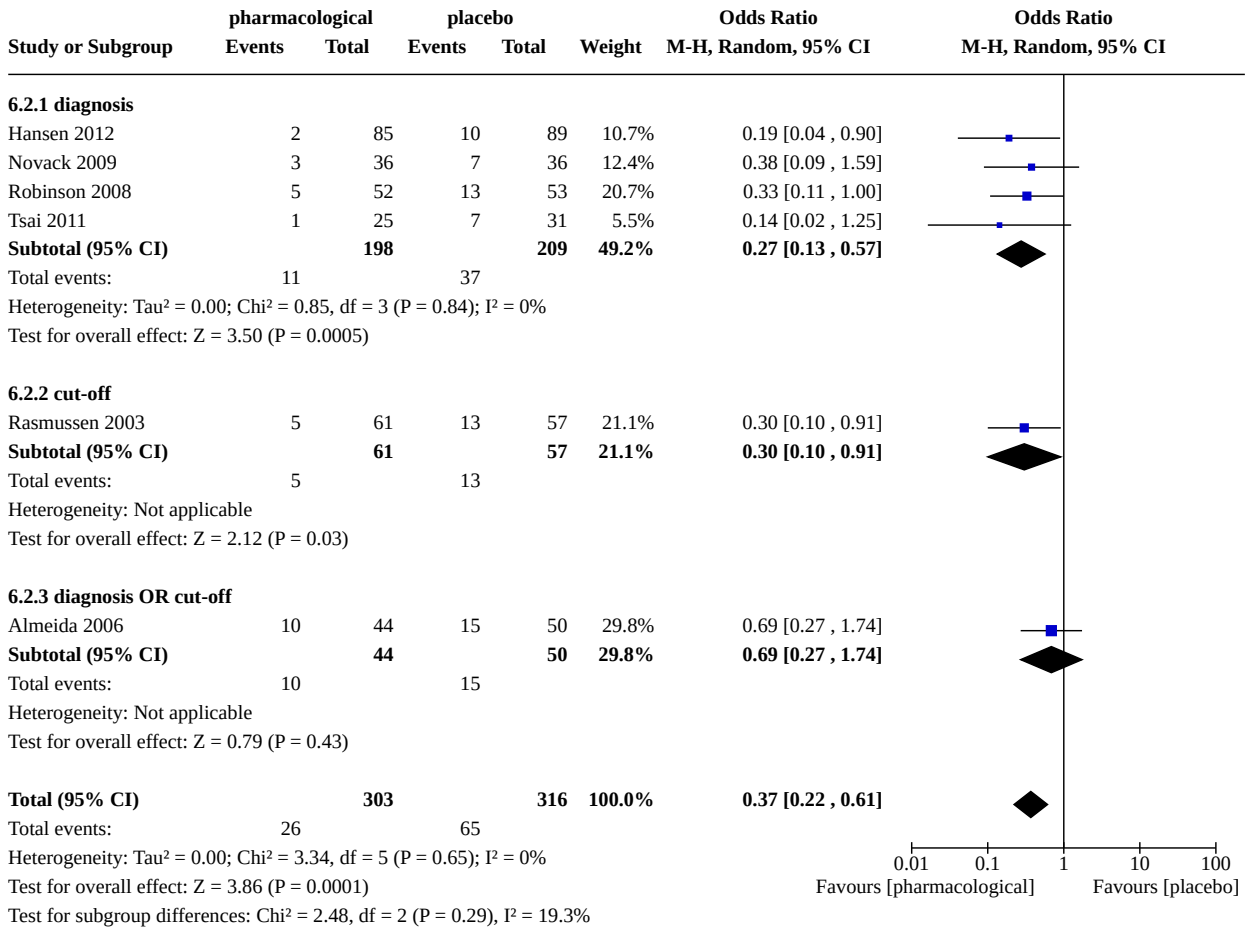
Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
6.3.1 diagnosis							
Robinson 2008	4	34	0	33	100.0%	9.89 [0.51 , 191.27]	
Subtotal (95% CI)		**34**		**33**	**100.0%**	**9.89 [0.51 , 191.27]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
Total (95% CI)		**34**		**33**	**100.0%**	**9.89 [0.51 , 191.27]**	
Total events:	4		0				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
Test for subgroup differences: Not applicable							

0.001 0.1 1 10 1000
Favours [pharmacological]   Favours [placebo]

Comparison 7. Sensitivity analyses on type of funding - incidence of depression: pharmacological intervention versus placebo

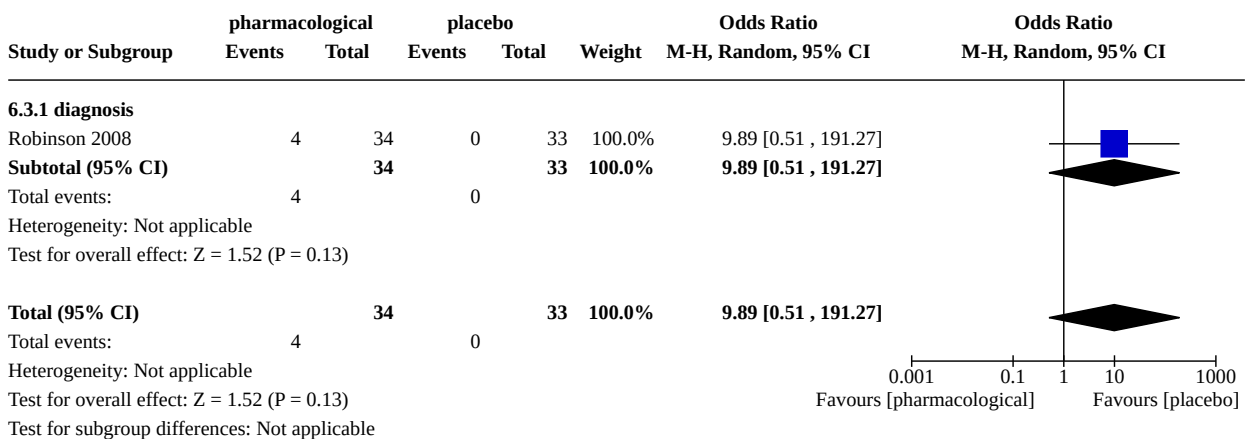| Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
7.1 post-intervention	7	591	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.18, 0.54]
7.1.1 diagnosis	4	369	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.09, 0.54]
7.1.2 cut-off	2	123	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.06, 0.72]
7.1.3 diagnosis OR cut-off	1	99	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.26, 2.00]
7.2 medium-term	2	166	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.26, 1.26]
7.2.1 diagnosis	1	72	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.09, 1.59]
7.2.2 diagnosis OR cut-off	1	94	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.27, 1.74]

Analysis 7.1. Comparison 7: Sensitivity analyses on type of funding - incidence of depression: pharmacological intervention versus placebo, Outcome 1: post-intervention

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
7.1.1 diagnosis						
Hansen 2012	2	85	10	89	12.2%	0.19 [0.04 , 0.90]
Narushima 2002	4	28	5	15	12.9%	0.33 [0.07 , 1.51]
Novack 2009	0	48	3	48	3.3%	0.13 [0.01 , 2.67]
Tsai 2011	1	25	7	31	6.3%	0.14 [0.02 , 1.25]
Subtotal (95% CI)		**186**		**183**	**34.7%**	**0.22 [0.09 , 0.54]**
Total events:	7		25			

Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 3 (P = 0.90); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
7.1.2 cut-off						
Hansen 2014	3	27	9	16	12.1%	0.10 [0.02 , 0.46]
Lydiatt 2013	6	36	16	44	25.1%	0.35 [0.12 , 1.02]
Subtotal (95% CI)		**63**		**60**	**37.2%**	**0.21 [0.06 , 0.72]**
Total events:	9		25			

Heterogeneity: Tau² = 0.36; Chi² = 1.77, df = 1 (P = 0.18); I² = 44%
Test for overall effect: Z = 2.49 (P = 0.01)

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
7.1.3 diagnosis OR cut-off						
Almeida 2006	8	48	11	51	28.0%	0.73 [0.26 , 2.00]
Subtotal (95% CI)		**48**		**51**	**28.0%**	**0.73 [0.26 , 2.00]**
Total events:	8		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.62 (P = 0.54)

Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Total (95% CI)		**297**		**294**	**100.0%**	**0.31 [0.18 , 0.54]**
Total events:	24		61			

Heterogeneity: Tau² = 0.01; Chi² = 6.13, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 4.19 (P < 0.0001)
Test for subgroup differences: Chi² = 3.69, df = 2 (P = 0.16), I² = 45.8%

Favours [pharmacological]   Favours [placebo]

Analysis 7.2. Comparison 7: Sensitivity analyses on type of funding - incidence of depression: pharmacological intervention versus placebo, Outcome 2: medium-term

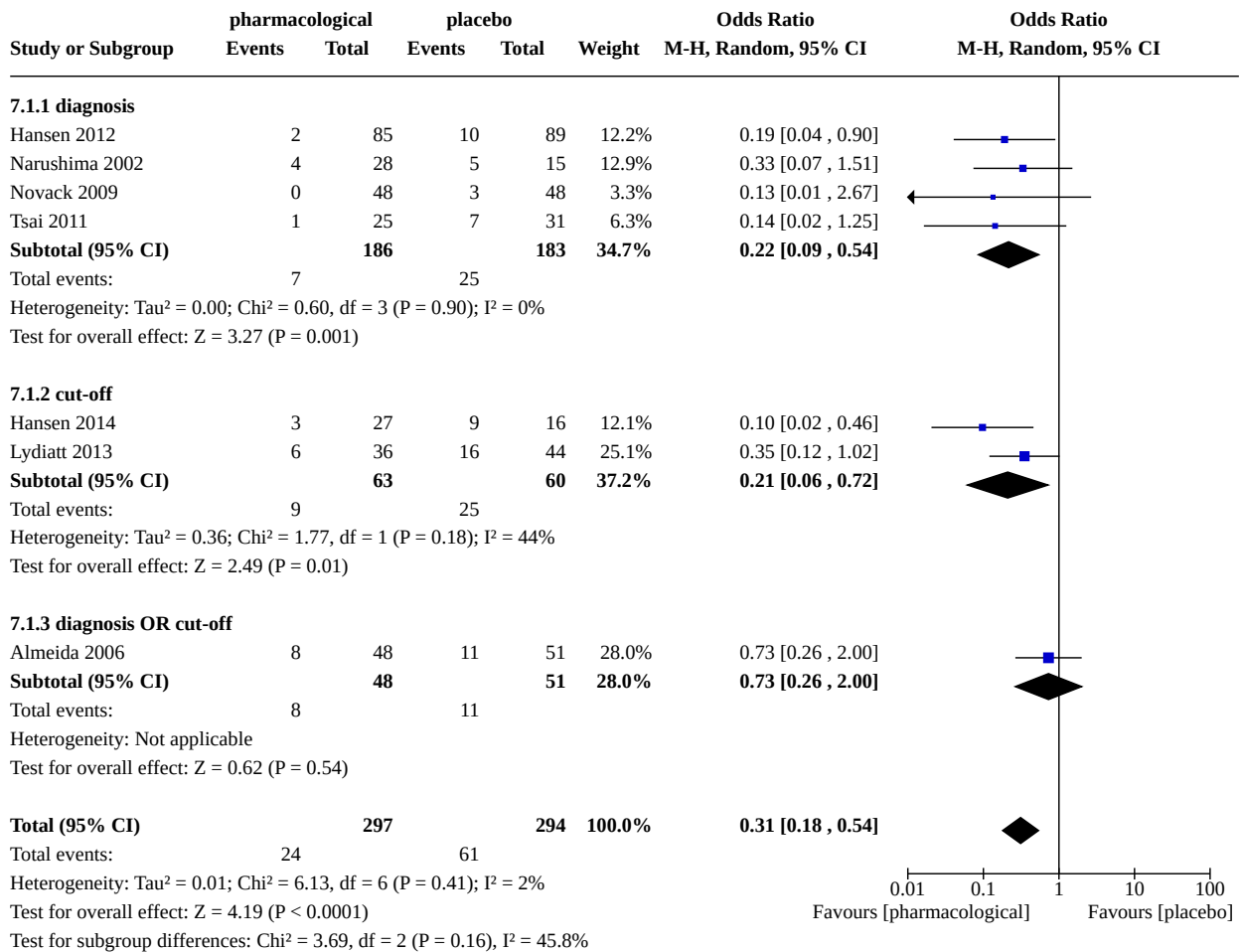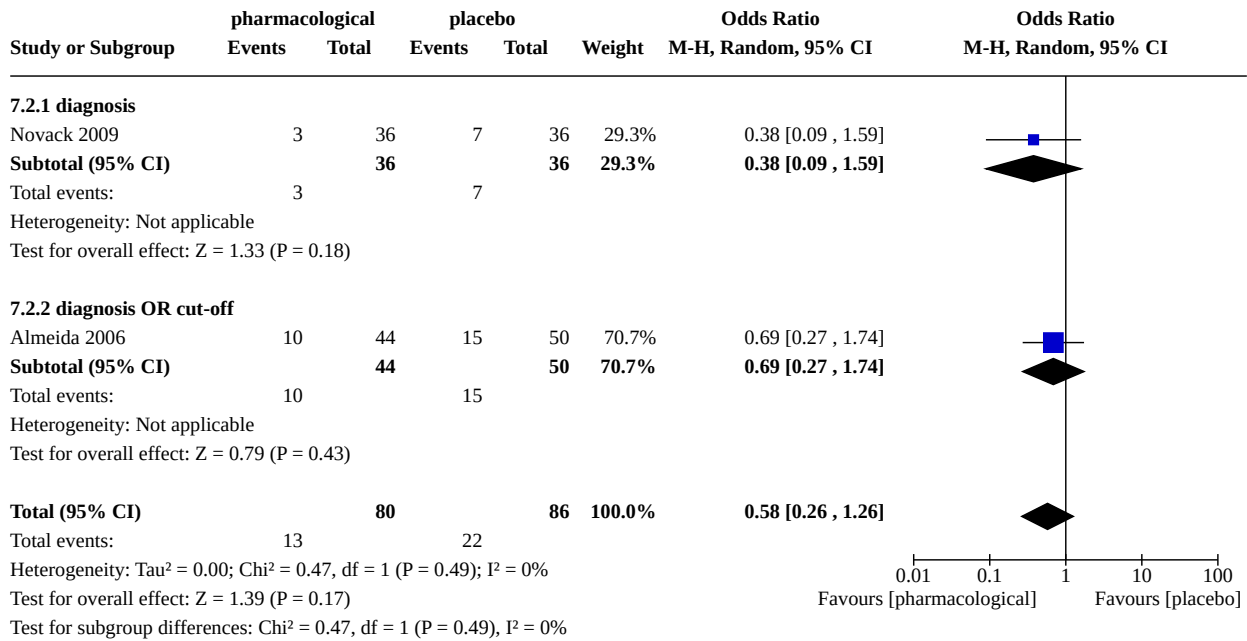| Study or Subgroup	pharmacological Events	Total	placebo Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
7.2.1 diagnosis							
Novack 2009	3	36	7	36	29.3%	0.38 [0.09 , 1.59]	
Subtotal (95% CI)		**36**		**36**	**29.3%**	**0.38 [0.09 , 1.59]**	
Total events:	3		7				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.33 (P = 0.18)							
7.2.2 diagnosis OR cut-off							
Almeida 2006	10	44	15	50	70.7%	0.69 [0.27 , 1.74]	
Subtotal (95% CI)		**44**		**50**	**70.7%**	**0.69 [0.27 , 1.74]**	
Total events:	10		15				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							
Total (95% CI)		**80**		**86**	**100.0%**	**0.58 [0.26 , 1.26]**	
Total events:	13		22				

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.17)
Test for subgroup differences: Chi² = 0.47, df = 1 (P = 0.49), I² = 0%

0.01 0.1 1 10 100
Favours [pharmacological]   Favours [placebo]

APPENDICES

Appendix 1. List of chronic diseases according to ICD-10 code

ICD-10 Code	Long-term physical condition
A15-A19	Tuberculosis
A81	Poliomyelitis
B15-B19	Viral hepatitis
B20-B24	Human immunodeficiency virus [HIV] disease
C00-D48	Malignant Neoplasms
E03, E05	Hypothyroidism
E10-E14	Diabetes mellitus
E24	Cushing syndrome
E66	Obesity
F01-F03	Dementia
G20	Parkinson disease

(Continued)

G23	Other degenerative diseases of basal ganglia
G24	Dystonia
G25	Extrapyramidal and movement disorders
G30; F00	Alzheimer disease
G31.0	Circumscribed brain atrophy
G31.0, F02.0	Frontotemporal dementia
G31.0, F02.0	Pick disease
G35	Multiple sclerosis
G40	Epilepsy
G43	Migraine
G44.2	Tension-type headache
G47	Sleep disorders
G62, G63	Polyneuropathy
G70	Myasthenia gravis
G81	Hemiplegia
G82	Paraplegia
G82	Tetraplegia
G93.3	Fatigue syndrome
H35.3	Macula Degeneration
H81	Disorders of vestibular function
H81	Otosclerosis
H90-H91	Hearing loss
I10-I15	Hypertensive diseases (Hypertension)
I20-I25	Ischaemic heart diseases
I20	Angina pectoris
I21-I22	Myocardial infarction
I42	Cardiomyopathy
I50	Heart failure

(Continued)

I60-I69	Cerebrovascular diseases
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Intracranial haemorrhage
I63	Cerebral infarction
I64	Stroke
I65	Occlusion of precerebral arteries
I65	Stenosis of precerebral arteries
I66	Occlusion of cerebral arteries
I66	Stenosis of cerebral arteries
I73.9	Peripheral vascular disease
I95	Hypotension
J40-J42	Chronic bronchitis
J43	Emphysema
J44	Chronic obstructive pulmonary disease
J45, J46	Asthma
J47	Bronchiectasis
J60-J70	Lung diseases due to external agents
J60-J65	Pneumoconiosis
K25	Gastric ulcer
K26	Duodenal ulcer
K29	Gastritis and duodenitis
K50	Crohn disease
K51	Ulcerative colitis
K58	Irritable bowel syndrome
K70-K77	Liver diseases
K72.1	Chronic hepatic failure
K74	Fibrosis and cirrhosis of liver

K86.1	Chronic Pancreatitis
L40-L41	Papulosquamous disorders
L41	Parapsoriasis
L93	Lupus erythematosus
M00-M99	Musculoskeletal disorders
M00-M25	Arthropathies
M05, M06	Rheumatoid arthritis
M05-M14	Polyarthropathies
M08, M09	Arthritis
M10	Gout
M15	Polyarthrosis
M15-M19	Arthrosis; Osteoarthrosis; Osteoarthritis
M16	Coxarthrosis
M30-M36	Systemic disorders of connective tissue
M30	Polyarteritis nodosa
M31	Necrotizing vasculopathies
M32	Systemic lupus erythematosus
M33	Dermatopolymyositis
M34	Systemic sclerosis
M40	Kyphosis and lordosis
M40-M43; M50-M54	Dorsopathies
M41	Scoliosis
M42	Spinal osteochondrosis
M45-M49	Spondylopathies
M54.5	Low back pain
M79.7	Fibromyalgia
M80-M85	Disorders of bone density and structure
M80-M82	Osteoporosis

(Continued)

N00-N08	Glomerular diseases
N02	Haematuria
N03	Chronic nephritic syndrome
N04	Nephrotic syndrome
N18	Chronic kidney disease
N30.2	Chronic cystitis
N41.1	Chronic prostatitis
N80	Endometriosis

Appendix 2. Cochrane Specialized Register

Cochrane Common Mental Disorders Controlled Trials Register (CCMDCTR)

The Cochrane Common Mental Disorders Group (CCMD) maintains an archived controlled trials register known as the CCMDCTR. This specialized register contains over 40,000 reference records (reports of RCTs) for anxiety disorders, depression, bipolar disorder, eating disorders, self-harm, and other mental disorders within the scope of this Group. The CCMDCTR is a partially studies-based register, with more than 50% of reference records tagged to around 12,500 individually PICO-coded study records. Reports of studies in the register were collated from (weekly) generic searches of key bibliographic databases to June 2016, which included: MEDLINE (1950 onwards), Embase (1974 onwards), PsycINFO (1967 onwards), quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), and review-specific searches of additional databases. Reports of studies were also sourced from international trials registries, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies (used to identify RCTs) are on the Group's website, with an example of the core MEDLINE search displayed below.

[MeSH Headings]: eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/ OR *[Title/ Author Keywords]:* (eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati#ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).tw,kf. AND *[RCT filter]:* (controlled clinical trial.pt. or randomised controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomised controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

Records were screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs were tagged to the appropriate study record.

The rationale of maintaining a comprehensive specialised register was reviewed when the editorial group moved from the University of Bristol to the University of York in June 2016. At this time, the Group decided to archive the CCMDCTR and return to searching the medical and psychological literature directly, on a review-by-review basis.

****

For this review the CCMDCTR was searched (all years to June 2016) using the following terms:

CCMDCTR-Studies Register:
Age Group = (adult or aged or unclear or "not stated") and *Condition or Comorbidity* = (depress*) and *Comorbidity field* = (not empty)
[depress*:SCO and (adult or aged or unclear or "not stated"):XAGE and not empty:SCM]
Studies including participants with physical comorbidities were manually selected.

CCMDCTR-References Register:
The references register was searched using a precision maximizing strategy (all years to 17 June 2016) to identify additional untagged/ uncoded references.

#1. ((prevent* or prophyl* or reduc* or relaps* or risk) NEAR depress*):ti,ab,kw,ky,emt,mh,mc
#2. (depress* or mental or mood or well being or "well being" or "quality of life"):ti
#3. (("chronic disease" or (chronic* NEAR2 (ill* or condition*1 or disease* or disorder* or health))) not "chronic depression"):ti
#4. ("physical* ill*" or "medical* ill*" or (long term NEXT (condition*1 or sick*)) or "medical* morbid*" or (medical* NEXT (comorbid* or co morbid*)) or multimorbid* or (multi* NEXT (morbid* or "co morbid*" or comorbid* or physical))):ti
#5.(Alzheimer* or angina or aneurysm or "ankylosing spondylitis" or arthropath* or arthriti* or arthrosis or arthroses or asthma* or "atrial fibrillation" or "autoimmune disease*" or "back pain" or blindness or "brain atroph*" or (bone NEXT (disease* or disorder*)) or ((bronchi* or bowel) NEXT (disease* or disorder*)) or bypass or (cancer or neoplasm* or neoplastic or malignan*) or (cardiac NEXT (arrest or arrhythmia* or surg*)) or cardiomyopath* or ((cardiovascular or coronary) NEAR2 (disease* or disorder* or event*)) or (cerebrovascular NEAR2 (disease* or disorder* or event*)) or "chronic obstructive" or COPD or (chronic NEAR2 pain) or cirrhosis or colitis or "congenital abnormalit*" or coxarthrosis or Crohn* or Cushing* or cystitis):ti
#6. (deformit* or disabled or (physical NEXT (deform* or disab* or impair*)) or *degenerative or dement* or dermato* or dorsopath* or diabet* or "digestive system*" or duoden* or dystonia or eczema or (endocrine NEXT (disease* or disorder*)) or emphysema or endometriosis or epilep* or extrapyramidal or "eye disease*" or ("fatigue syndrome" or "chronic fatigue") or fibromyalgia or fibrosis or (gastr* NEXT (disease* or disorder*)) or gastritis or gout or (glomerul* NEXT (disease* or disorder*)) or headache* or ((h?emic or lymph*) NEXT (disease* or disorder*)) or h?ematuria or h?emophili* or h?emorrhage or ((hearing or visual or vision) NEAR2 (aid* or impair* or loss)) or hemiplegi* or hepatitis or h?emodialysis or ((renal or kidney) NEXT (disease* or disorder* or failure)) or (heart NEXT (attack* or disease* or disorder* or failure or surg*)) or HIV or "human immunodeficiency virus" or hypertensi* or hypotensi*):ti
#7. ("inflammatory disease*" or incontinen* or "irritable bowel" or isch?emi* or (joint NEXT (disease* or disorder*)) or kyphosis or leuk? emia or ((liver or hepatic) NEXT (disease* or disorder* or failure)) or lordosis or "lung disease*" or "lupus erythemat*" or lymphoma or "macular degeneration" or migraine* or "movement disorder*" or musculoskeletal or necrotizing or nephrotic* or neuromuscular or "multiple sclerosis" or "myasthenia gravis" or myeloma or "myocardial infarct*"):ti
#8. (((nutritional or metabolic) NEXT (disease* or disorder or syndrome*)) or (organ* NEAR2 (transplant* or recipient*)) or (neurological NEXT (disease* or disorder*)) or "occupational disease*" or occlusion* or obesity or orthop?edic* or osteo* or otorhinolaryngology* or otosclerosis or pancrea* or papulosquamous or paraplegi* or Parkinson's* or "peripheral vascular" or "pick disease*" or pneumoconiosis or polio* or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or prostat* or psoriasis or parapsoriasis or (pulmonary NEAR2 (disease* or disorder*))):ti
#9. ((respiratory NEXT (disease* or disorder*)) or rheumat* or sclerosis or scoliosis or ((skin or "connective tissue") NEXT (disease* or disorder*)) or ("sleep disorder*" or "sleep apn?ea" or insomnia* or dyssomnia* or hypersomnia*) or spondylo* or stenosis* or stoma* or (stroke or strokes or poststroke or "cerebral infarct*") or tetraplegi* or ((thyroid NEAR (disease* or disorder* or dysfunction*)) or hyperthyroidism or hypothyroidism) or tuberculosis or (systemic NEAR (disorder* or disease*)) or ulcer* or (urogenital NEXT (disease* or disorder*)) or vasculopath* or (vascular NEAR (disease* or disorder*)) or vestibular or ((virus or viral) NEXT disease)):ti
#10. syndrome*:ti
#11.((depress* or mood) and ((*agia or *algia or *dynia or *emia or *enia or *itis or *oma or *omata or *omnia or *opath* or *osis or *oses or *penia or *phagy or *philia or *plasia or *plasty or *plegi* or *rrhag* or *trophy) not (diagnos* or doses or hypnos* or neuros* or psychos* or psychopath* or prognos* or schizophreni*))):ti
#12. (((#1 or #2) and (#3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)) or #11)
#13. ((depress* or mood) and prevent* and (intervention or program* or strategy or study or *therap* or treat* or train* or trial)):ti
#14. *(Lines #4 to #9):all fields*
#15. ((#13 and #14) or #12)
[Note:The strategy reported in the protocol was too sensitive, retrieving a lot of noise around treatment studies and chronic depression.]

Appendix 3. Biomedical database search strategies

1. COCHRANE LIBRARY (Reviews and Trials (CENTRAL))

The Cochrane Library was searched (all years to Issue 11, November 2014 and again in November 2017 and again in February 2020) using the following terms:

[Depression prevention]
#1. ((prevent* or prophyl* or reduc* or relaps* or risk) near depress*):ti,ab
#2. MeSH descriptor: [DEPRESSION] this term only and with qualifier(s): [Prevention & control - PC]
#3. MeSH descriptor: [DEPRESSIVE DISORDER] this term only and with qualifier(s): [Prevention & control - PC]
#4. MeSH descriptor: [DEPRESSIVE DISORDER, MAJOR] this term only and with qualifier(s): [Prevention & control - PC]
#5. ((depress* or dysthymi* or affective disorder* or affective symptom* or melanchol* or mood) near/3 (first episode* or onset or prevent* or relaps* or recurr* or risk or at-risk or symptom*)):ti,ab
#6. (depress* near/3 (subclinical* or sub-clinical* or subthreshold* or sub-threshold* or subsyndrom* or sub-syndrom*)):ti,ab
#7. ((mild* or minor or nonmajor or non major) next depress*):ti,ab
#8. "low mood*"
#9. (depress* or mood):ti and (prevent* near/2 (primary or tertiary or universal or selective or indicated)):ti,ab
#10. (depressi* or depressed):ti
#11. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
[Chronic physical illness]
#12. MeSH descriptor: [CHRONIC DISEASE] this term only
#13. (("chronic disease" or (chronic* near/3 (ill* or condition*1 or disease* or disorder* or health))) not "chronic depression")
#14. ("physical* ill*" or "medical* ill*")
#15. ("long term" next (condition* or sick*))
#16. ("medical* morbid*" or (medical* next (comorbid* or "co morbid*")))
#17. (multimorbid* or (multi* next (morbid* or "co morbid*" or comorbid* or physical)))
#18. (Alzheimer* or angina or aneurysm or "ankylosing spondylitis" or arthropath* or arthriti* or arthrosis or arthroses or asthma* or "atrial fibrillation" or "autoimmune disease*" or "back pain" or blindness or "brain atroph*" or (bone next (disease* or disorder*)) or bronchi* or (bowel next (disease* or disorder*)) or bypass or (cancer or neoplasm* or neoplastic or malignan*) or (cardiac next (arrest or arrhythmia* or surg*)) or cardiomyopath* or ((cardiovascular or coronary) near/3 (disease* or disorder* or event*)) or (cerebrovascular near/3 (disease* or disorder* or event*)) or "chronic obstructive" or COPD or (chronic near/3 pain) or cirrhosis or colitis or "congenital abnormalit*" or coxarthrosis or Crohn* or Cushing* or cystitis or disabled or (physical* near/3 (deform* or disab* or impair*)) or (degenerative or neurodegenerative) or dementia or dermato* or dorsopath* or diabet* or "digestive system*" or duoden* or dystonia or eczema or (endocrine next (disease* or disorder*)) or emphysema or endometriosis or epilepsy or extrapyramidal or "eye disease*" or ("fatigue syndrome" or "chronic fatigue") or fibromyalgia or fibrosis or (gastr* next (disease* or disorder*)) or gastritis or gout or (glomerul* next (disease* or disorder*)) or headache* or ((hemic or haemic or lymph*) next (disease* or disorder*)) or hematuria or haematuria or hemophili* haemophili* or hemorrhag* or haemorrhag* or ((hearing or visual or vision) near/3 (aid* or impair* or loss)) or hemiplegi* or hepatitis or hemodialysis or haemodialysis or ((renal or kidney) next (disease* or disorder* or failure)) or (heart next (attack* or disease* or disorder* or failure or surg*)) or HIV or "human immunodeficiency virus" or hypertensi* or hypotensi* or "inflammatory disease*" or incontinen* or "irritable bowel" or ischemi* or ischaemi* or (joint next (disease* or disorder*)) or kyphosis or leukemia or leukaemia or ((liver or hepatic) next (disease* or disorder* or failure)) or lordosis or "lung disease*" or "Lupus erythemat*" or lymphoma or "macular degeneration" or migraine* or "movement disorder*" or musculoskeletal or necrotizing or nephrotic* or neuromuscular or ((nutritional or metabolic) next (disease* or disorder or syndrome*)) or "multiple sclerosis" or "Myasthenia gravis" or myeloma or "myocardial infarction" or (organ* near/3 (transplant* or recipient*)) or (neurological next (disease* or disorder*)) or "occupational disease*" or occlusion* or obesity or orthopedic* or orthopaedic* or osteo* or otorhinolaryngology or otosclerosis or pancrea* or papulosquamous or paraplegi* or Parkinson* or "peripheral vascular" or "Pick disease*" or pneumoconiosis or polio* or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or prostat* or psoriasis or parapsoriasis or (pulmonary near/3 (disease* or disorder*)) or (respiratory next (disease* or disorder*)) or rheumat* or sclerosis or scoliosis or (sleep disorder* or "sleep apn*ea" or "sleep apnaea" insomnia* or dyssomnia* or hypersomnia*) or spondylo* or stenosis* or (stroke or strokes or poststroke or cerebral infarct*) or tetraplegi* or ((thyroid next (disease* or disorder* or dysfunction*)) or hyperthyroidism or hypothyroidism) or tuberculosis or (systemic next (disorder* or disease*)) or ulcer* or (urogenital next (disease* or disorder*)) or vasculopath* or (vascular next (disease* or disorder*)) or vestibular or ((virus or viral) next disease))
#19. MeSH descriptor: [NEOPLASMS] explode all trees
#20. MeSH descriptor: [MUSCULOSKELETAL DISEASES] explode all trees
#21. MeSH descriptor: [DIGESTIVE SYSTEM DISEASES] explode all trees
#22. MeSH descriptor: [RESPIRATORY TRACT DISEASES] explode all trees
#23. MeSH descriptor: [STOMATOGNATHIC DISEASES] explode all trees
#24. MeSH descriptor: [OTORHINOLARYNGOLOGIC DISEASES] explode all trees
#25. MeSH descriptor: [NERVOUS SYSTEM DISEASES] explode all trees
#26. MeSH descriptor: [EYE DISEASES] explode all trees
#27. MeSH descriptor: [MALE UROGENITAL DISEASES] explode all trees
#28. MeSH descriptor: [FEMALE UROGENITAL DISEASES] explode all trees
#29. MeSH descriptor: [CARDIOVASCULAR DISEASES] explode all trees
#30. MeSH descriptor: [HEMIC AND LYMPHATIC DISEASES] explode all trees
#31. MeSH descriptor: [SKIN AND CONNECTIVE TISSUE DISEASES] explode all trees

Cochrane
Library

Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

#32. MeSH descriptor: [NUTRITIONAL AND METABOLIC DISEASES] explode all trees

#33. MeSH descriptor: [ENDOCRINE SYSTEM DISEASES] explode all trees

#34. MeSH descriptor: [IMMUNE SYSTEM DISEASES] explode all trees

#35. MeSH descriptor: [DISORDERS OF ENVIRONMENTAL ORIGIN] explode all trees

#36. MeSH descriptor: [PATHOLOGICAL CONDITIONS, SIGNS AND SYMPTOMS] explode all trees

#37. MeSH descriptor: [OCCUPATIONAL DISEASES] explode all trees

#38. MeSH descriptor: [VIRUS DISEASES] explode all trees

#39. syndrome*:ti,ab,kw

#40. MeSH descriptor: [QUALITY OF LIFE] this term only and with qualifier(s): [Psychology - PX]

#41. MeSH descriptor: [REHABILITATION] this term only and with qualifier(s): [Psychology - PX]

#42. MeSH descriptor: [ADAPTATION, PSYCHOLOGICAL] explode all trees

#43. (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39)

[Combing search sets - depression prevention + chronic physical illness]

#44. #11 and #43

#45. (#1 or #2 or #3 or #4) and (#12 or #13)

#46. #10 and (#40 or #41 or #42)

#47. (#44 or #45 or #46)

[INTERVENTIONS: Psychological interventions]

#48. MeSH descriptor: [PSYCHOTHERAPY] explode all trees

#49. ((psychologic* or behavior or behaviour or cognitive) near/3 (intervent* or therap* or treat* or manag*))

#50. (abreaction or "acting out" or "acceptance and commitment" or "activity scheduling" or adlerian or "age regression" or "analytical therap*" or "anger control" or "anger management" or "art therap*" or "assertive* training" or "attention bias modification" or "autogenic training" or autosuggestion or "aversion therap*" or "balint group" or "behavio* activation" or "behavio* contracting" or "behavio* modification" or "behavio* therap*" or bibliotherap* or biofeedback or "body therap*" or "brief therapy" or "caregiver support" or catharsis or "client cent* therapy" or "cognitive behavio* therap*" or "cognitive therap*" or CBT or cCBT or iCBT or "cognitive behavio* stress management" or "cognitive rehabilitation" or "cognitive restructur*" or "colo* therap*" or "compassion focus*" or "compassionate therap*" or "conjoint therap*" or "contingency management" or "conversion therap*" or "conversational therap*" or countertransference or "coping skill*" or counsel* or "couples therap*" or "covert sensitization" or "crisis intervention" or "dance therap*" or (dialectic* near/2 therap*) or "diffusion therap*" or "distraction therap*" or "drama therapy" or (dream* near/2 analys*) or "eclectic therap*" or "emotion* focus* therap*" or "emotional freedom technique" or "encounter group therap*" or existential or experiential or "exposure therap*" or "expressive therap*" or "eye movement desensiti*" or "family therap*" or "feminist therap*" or "focus oriented" or "free association" or freudian or "functional analysis" or "geriatric therap*" or gestalt or griefwork or "group therap*" or "guided image*" or "holistic therap*" or humanistic or hypnosis or hypnotherapy or hypnoti* or "implosive therap*" or "insight therap*" or "integrative therap*" or "interpersonal therap*" or Jungian or kleinian or logotherap* or "logo therap*" or "marathon group therap*" or "marital therap*" or meditation or "mental healing" or metacognitive or meta-cognitive or milieu or "mind train*" or mindfulness or morita or "multimodal therap*" or music or "narrative therap*" or "nondirective therap*" or non-directive therap* or "nondirective therap*" or "non-specific therap*" or "nonspecific therap*" or "object relations" or "personal construct therap*" or "person cent* therap*" or "persuasion therap*" or "pet therap*" or "play therap*" or ((pleasant or pleasing) near/2 event*) or "present cent* therap*" or "primal therap*" or "problem focus* therap*" or "problem sol*" or "process experiential" or psychoanaly* or psychodrama or psychodynamic or psychoeducat* or psychotherap* or "rational emotive" or "reality therap*" or "reciprocal inhibition" or "relationship therap*" or relaxation or "reminiscence therap*" or rogerian or "role play*" or schema or "self analys*" or "self esteem building" or "sensitivity training" or "sex therap*" or "sleep phase chronotherap*" or "socioenvironment* therap*" or "social skill*" or sociotherap* or "solution focused" or "stress management" or "support group*" or (support near/2 psycho*) or "supportive therap*" or "systematic desensit*" or "systemic * therap*" or "therapeutic communit*" or "therapeutic technique" or "third wave" or "time limited therap*" or "transference therap*" or "transactional analysis" or transtheoretical or "validation therap*")

#51. (#48 or #49 or #50)

[INTERVENTIONS: Antidepressants]

#52. MeSH descriptor: [ANTIDEPRESSIVE AGENTS] explode all trees

#53. MeSH descriptor: [NEUROTRANSMITTER UPTAKE INHIBITORS] explode all trees

#54. MeSH descriptor: [MONOAMINE OXIDASE INHIBITORS] explode all trees

#55. (antidepress* or "anti depress*" or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic*)

#56. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin* or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin* or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine

or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin* or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin* or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromin* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone)
#57. #52 or #53 or #54 or #55 or #56
[Combing search sets - depression prevention + chronic physical illness + intervention]
#58. (#47 and (#51 or #57))
#59. ((depress* or mood) and prevent* and (intervention or program* or *therap* or strategy or study or trial)):ti
#60. (depress* or mood):ti and (prevent* near/2 (primary or tertiary or universal or selective or indicated)):ti,ab
#61. (#59 or #60) and #43
#62. #58 or #61
[Results, 2014: CENTRAL(Trials)=2944; CDSR=148 ; DARE=40 ;HTA=2; NHS-EED=21]

In 2017, the following exclusion criteria was added to the search:
NOT *(schizo* or ((severe or outpatient or inpatient) near/2 psychiatric) or suicid* or bipolar or psychosis or ((resistant or refractory) next depress*) or (treatment near/2 (major depress*)) or PTSD or "posttraumatic stress disorder" or "post traumatic stress disorder" or ((postpartum or post-partum or postnatal or post-natal) next depress*) or electroconvulsive or rTMS):ti*

2. OVID MEDLINE was search (from 1 January 2004 to 6 February 2020) using the following terms:

[Physical illness]
1. (physical* ill* or medical* ill*).tw.
2. CHRONIC DISEASE/
3. (chronic* adj2 (ill* or condition*1 or disease* or disorder* or health)).tw.
4. (long term adj (condition*1 or sick*)).tw.
5. (medical* morbid* or (medical* adj (comorbid* or co morbid*))).tw.
6. (multimorbid* or (multi* adj (morbid* or co morbid* or comorbid* or physical))).tw.
7. exp NEOPLASMS/ or exp MUSCULOSKELETAL DISEASES/ or exp DIGESTIVE SYSTEM DISEASES/ or exp STOMATOGNATHIC DISEASES/ or exp RESPIRATORY TRACT DISEASES/ or exp OTORHINOLARYNGOLOGIC DISEASES/ or exp NERVOUS SYSTEM DISEASES/ or exp EYE DISEASES/ or exp MALE UROGENITAL DISEASES/ or exp FEMALE UROGENITAL DISEASES/ or exp CARDIOVASCULAR DISEASES/ or exp "HEMIC AND LYMPHATIC DISEASES"/ or exp "SKIN AND CONNECTIVE TISSUE DISEASES"/ or exp "NUTRITIONAL AND METABOLIC DISEASES"/ or exp ENDOCRINE SYSTEM DISEASES/ or exp IMMUNE SYSTEM DISEASES/ or exp "DISORDERS OF ENVIRONMENTAL ORIGIN"/ or exp "PATHOLOGICAL CONDITIONS, SIGNS AND SYMPTOMS"/ or exp OCCUPATIONAL DISEASES/ or exp VIRUS DISEASES/
8. (Alzheimer* or angina or aneurysm or ankylosing spondylitis or arthropath* or arthriti* or arthrosis or arthroses or asthma* or atrial fibrillation or autoimmune disease* or back pain or blindness or brain atroph* or (bone adj (disease* or disorder*)) or bronchi* or (bowel adj (disease* or disorder*)) or bypass or (cancer or neoplasm* or neoplastic or malignan*) or (cardiac adj (arrest or arrhythmia* or surg*)) or cardiomyopath* or ((cardiovascular or coronary) adj2 (disease* or disorder* or event*)) or (cerebrovascular adj2 (disease* or disorder* or event*)) or chronic obstructive or COPD or (chronic adj2 pain) or cirrhosis or colitis or congenital abnormalit* or coxarthrosis or Crohn*1 or Cushing*1 or cystitis or disabled or (physical* adj2 (deform* or disab* or impair*)) or (degenerative or neurodegenerative) or dementia or dermato* or dorsopath* or diabet* or digestive system* or duoden* or dystonia or eczema or (endocrine adj (disease* or disorder*)) or emphysema or endometriosis or epilepsy or extrapyramidal or eye disease* or (fatigue syndrome or chronic fatigue) or fibromyalgia or fibrosis or (gastr* adj (disease* or disorder*)) or gastritis or gout or (glomerul* adj (disease* or disorder*)) or headache* or ((h?emic or lymph*) adj (disease* or disorder*)) or h?ematuria or h?emophili* or h?emorrhage or ((hearing or visual or vision) adj2 (aid*1 or impairment* or loss)) or hemiplegi* or hepatitis or h?emodialysis or ((renal or kidney) adj (disease* or disorder* or failure)) or (heart adj (attack* or disease* or disorder* or failure or surg*)) or HIV or human immunodeficiency virus or hypertensi* or hypotensi* or inflammatory disease* or incontinen* or irritable bowel or isch?emi* or (joint adj (disease* or disorder*)) or kyphosis or leuk?emia or ((liver or hepatic) adj (disease* or disorder* or failure)) or lordosis or lung disease* or Lupus erythemat* or lymphoma or macular degeneration or migraine* or movement disorder* or musculoskeletal or necrotizing or nephrotic* or neuromuscular or ((nutritional or metabolic) adj (disease* or disorder or syndrome*)) or multiple sclerosis or Myasthenia gravis or myeloma or myocardial infarction or (organ*1 adj2 (transplant* or recipient*)) or (neurological adj (disease* or disorder*)) or occupational disease* or occlusion* or obesity or orthop?edic* or osteo* or otorhinolaryngology or otosclerosis or pancrea* or papulosquamous or paraplegi* or Parkinson* or peripheral vascular or Pick disease* or pneumoconiosis or polio* or polyarthropath* or polyarteritis or polyarthrosis or polyneuropath* or prostat* or psoriasis or parapsoriasis or (pulmonary adj2 (disease* or disorder*)) or (respiratory adj (disease* or disorder*)) or rheumat* or sclerosis or scoliosis or (sleep disorder* or sleep apn?ea or insomnia* or dyssomnia* or hypersomnia*) or spondylo* or stenosis* or (stroke or strokes or poststroke or cerebral infarct*) or tetraplegi* or ((thyroid adj (disease* or disorder* or dysfunction*)) or hyperthyroidism or hypothyroidism) or tuberculosis or (systemic adj (disorder* or disease*)) or ulcer* or (urogenital adj (disease* or disorder*)) or vasculopath* or (vascular adj (disease* or disorder*)) or vestibular or ((virus or viral) adj disease)).mp.
9. syndrome*1.mp.
10. or/1-9
[Depression prevention]
11. DEPRESSION/pc [prevention & control]

12. DEPRESSIVE DISORDER/pc [prevention & control]
13. DEPRESSIVE DISORDER, MAJOR/pc [prevention & control]
14. *MENTAL HEALTH/
15. ((depress* or dysthymi* or affective disorder* or affective symptom* or melanchol* or mood) adj2 (first episode* or onset or prevent* or relaps* or recurr* or risk or at-risk or symptom*)).tw.
16. (depress* adj2 (subclinical* or sub-clinical* or subthreshold* or sub-threshold* or subsyndrom* or sub-syndrom*)).tw.
17. ((mild* or minor or nonmajor or non major) adj depress*).tw.
18. low mood.tw.
19. (depressi* or depressed).ti. and (*"QUALITY of LIFE"/ or exp *REHABILITATION/ or ADAPTATION, PSYCHOLOGICAL/)
20. (depress* or mood).ti. and (prevent* adj1 (primary or tertiary or universal or selective or indicated)).ti,ab.
21. or/11-20
[RTC Filter - precision maximizing]
22. randomized controlled trial.pt.
23. (randomi#ed or RCT).ti,ab.
24. (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab.
25. placebo*.ab.
26. ((control* or group*1) and (waitlist* or wait* list* or treatment as usual or TAU)).ab.
27. trial.ti.
28. (animals not (humans and animals)).sh.
29. or/21-26
30. 28 not 27
31. (10 and 21 and 30)
32. (2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014*).ed,yr.
33. (31 and 32)
In 2017, the MEDLINE search results were limited to records containing the following terms:
(*(risk or predict* or prevent* or prophyla*).ti,ab,kf,hw. or (prevention & control).fs.) and (2014* or 2015* or 2016* or 2017*).yr,ed,dc,ep.*

In 2020, the MEDLINE search results were based on the 2017 restrictions and limited to records containing the following terms: (2017/11 or 2018* or 2019* or 2020*).yr,ed,dc,ep.

3. OVID EMBASE was searched (i) 2010 to 2014 and (ii) 2014 to 9 November 2017 and (iii) November 2017 to 6 February 2020, using the following terms:

[Physical illness]
1. (physical* ill* or medical* ill*).tw.
2. (chronic* adj2 (ill* or condition*1 or disease* or disorder* or health)).tw.
3. (long term adj (condition*1 or sick*)).tw.
4. (medical* morbid* or (medical* adj (comorbid* or co morbid*))).tw.
5. (multimorbid* or (multi* adj (morbid* or co morbid* or comordid* or physical))).tw.
6. CHRONIC DISEASE/
7. PHYSICAL DISEASE/ or exp PHYSICAL DISEASE BY ANATOMICAL STRUCTURE/ or exp PHYSICAL DISEASE BY BODY FUNCTION/ or exp "PHYSICAL DISEASE BY COMPOSITION OF BODY FLUIDS, EXCRETA AND SECRETIONS"/ or exp PHYSICAL DISEASE BY DEVELOPMENTAL AGE/ or exp "PHYSICAL DISEASE BY ETIOLOGY AND PATHOGENESIS"/
8. *ibid* line 8 of MEDLINE search
9. syndrome*1.mp.
10. or/1-9
[Depression prevention]
11. MOOD DIORDER/pc *[prevention & control]*
12. *DEPRESSION/pc or AGITATED DEPRESSION/pc or DYSTHYMIA/pc or INVOLUTIONAL DEPRESSION/pc or LATE LIFE DEPRESSION/pc or MAJOR DEPRESSION/pc or MASKED DEPRESSION/pc or "MIXED ANXIETY and DEPRESSION"/pc or "MIXED DEPRESSION AND DEMENTIA"/pc or ORGANIC DEPRESSION/pc or POSTOPERATIVE DEPRESSION/pc or REACTIVE DEPRESSION/pc
13. *MENTAL HEALTH/
14. ((depress* or dysthymi* or affective disorder* or affective symptom* or melanchol* or mood) adj2 (first episode* or onset or prevent* or relaps* or recurr* or risk or at-risk or symptom*)).tw.
15. (depress* adj2 (subclinical* or sub-clinical* or subthreshold* or sub-threshold* or subsyndrom* or sub-syndrom*)).tw.
16. ((mild* or minor or nonmajor or non major) adj depress*).tw.
17. low mood.tw.
18. (depressi* or depressed).ti. and (*QUALITY of LIFE/ or exp *REHABILITATION/)
19. (depress* or mood).ti. and (prevent* adj1 (primary or tertiary or universal or selective or indicated)).ti,ab.
20. or/11-19
[RTC Filter - precision maximizing]

Prevention of depression in adults with long-term physical conditions (Review)

21. randomized controlled trial.de.

22. (randomi#ed or RCT).ti,ab.

23. (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab.

24. placebo.de.

25. placebo*.ti,ab.

26. ((control* and group*1) and (waitlist* or wait* list* or treatment as usual or TAU)).ab.

27. controlled trial.ti.

28. ((animal or nonhuman) not (human and (animal or nonhuman))).de.

29. or/21-27

30. 29 not 28

31. (10 and 20 and 30)

In 2017, the EMBASE search results were limited to records containing the following terms:

((risk or predict* or prevent* or prophyla*).ti,ab,kw,hw. or (prevention).fs.) and (2014* or 2015* or 2016* or 2017*).yr,em.

The results were also limited to non-MEDLINE journals.

In 2020, the EMBASE search results were based on the 2017 restrictions and limited to records containing the following terms:

(2017/11 or 2018* or 2019* or 2020*).yr,em.

4. OVID PsycINFO was search (all years to 9 February 2020) using the following terms:

[Physical illness]

1. (physical* ill* or medical* ill*).ti,ab,id.

2. (chronic* adj2 (ill* or condition*1 or disease* or disorder* or health)).ti,ab,id.

3. (long term adj (condition*1 or sick*)).ti,ab,id.

4. (medical* morbid* or (medical* adj (comorbid* or co morbid*))).ti,ab,id.

5. (multimorbid* or (multi* adj (morbid* or co morbid* or comorbid* or physical))).tw.

6. CHRONIC ILLNESS/ or "CHRONICITY (Disorders)"/ or CHRONIC PAIN/ or CHRONIC FATIGUE SYNDROME/

7. exp PHYSICAL DISORDERS/

8. *ibid* line 8 of MEDLINE search *(.ti,ab,id,sh. PsycINFO fields only)*

9. syndrome*1.ti,ab,id,sh.

10. or/1-9

[Depression prevention]

11. (ATYPICAL DEPRESSION/ OR "DEPRESSION (EMOTION)"/ or MAJOR DEPRESSION/ or DYSTHYMIC DISORDER/ or ENDOGENOUS DEPRESSION/ or REACTIVE DEPRESSION/) and prevention.ti,ab,id,sh**.**

12. MENTAL HEALTH/

13. ((depress* or dysthymi* or affective disorder* or affective symptom* or melanchol* or mood) adj2 (first episode* or onset or prevent* or relaps* or recurr* or risk or at-risk or symptom*)).ti,ab,id.

14. (depress* adj2 (subclinical* or sub-clinical* or subthreshold* or sub-threshold* or subsyndrom* or sub-syndrom*)).ti,ab,id.

15. ((mild* or minor or nonmajor or non major) adj depress*).ti,ab,id.

16. low mood.ti,ab,id.

17. (depress* or mood).ti,id. and (REHABILITATION/ or OCCUPATIONAL THERAPY/ or "QUALITY OF LIFE"/ or LIFE CHANGES/ or LIFESTYLE CHANGES/)

18. (depress* or mood).ti,id. and (prevent* adj1 (primary or tertiary or universal or selective or indicated)).ti,ab,id.

19. or/11-18

[RTC Filter - precision maximizing]

20. treatment effectiveness evaluation.sh.

21. "2000".md.

22. randomi#ed.ti,ab,id.

23. (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab.

24. placebo*.ab,sh.

25. ((control* or group*1) and (waitlist* or wait* list* or treatment as usual or TAU)).ab.

26. trial.ti.

27. or/19-25

28. (10 and 19 and 27)

W H A T ' S   N E W

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Date	Event	Description
6 March 2021	Amended	Correction made to formatting of Figure 1 following a system error.

HISTORY

Protocol first published: Issue 8, 2014
Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

Drafting of protocol: HK, HB, WHJ, & OM
Developing of search strategy: HK, HB, WHJ, & OM
Trial search and selection: HK & OM
Data extraction: HK & OM
Entering data into RevMan: HK
Data analysis: HK
Drafting the review: HK, HB, JB, & OM

DECLARATIONS OF INTEREST

HK: None known
HB: None known
JB: None known
OM: None known

SOURCES OF SUPPORT

Internal sources

- Quality Management and Social Medicine, Germany

  Funding the review project

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes in authorship: After contributing to the protocol, WHJ was unavailable for the review. To ensure the quality of the review, we were very grateful to have JB join us as an author to offer his comprehensive expertise on medical and psychological aspects.

Title: In keeping with the terminology used by the CCMD group, we changed the title from 'Prevention of depression in chronically physically ill adults' to 'Prevention of depression in adults with long-term physical conditions.'

Types of participants - Diagnosis: in order to exclude adults with an initial major depressive order, assessment of major depression could also be made by scoring above a specific cut-off point on standardized, validated rating scales, or standardized, validated self-report questionnaires for depression.

Types of interventions - Experimental interventions: we added 'milnacipran' in the list of experimental interventions.

Types of outcome measures - Timing of outcome assessment: to use consistent phrasing throughout the review, we changed the term post-treatment into post-intervention.

Data extraction and management: In the protocol we stated that we would extract 'mean and standard deviation/error, effect sizes, confidence intervals (CIs), odds ratios (ORs), hazard ratios (HRs), risk ratios (RRs), P values'. We corrected this. It now says 'sample sizes, incidence, means, standard deviation/error, and P values'.

Measures of treatment effect: In the protocol the statement addressing the descriptive assessment of tolerability (adverse events) and acceptability (drop-outs) was under the heading 'dichotomous data'. We moved this to 'continuous data'.

Sensitivity analysis: To use consistent phrasing throughout the review, we changed the term post-treatment into post-intervention.

Dealing with missing data: In the protocol we stated that we would account for missing data 'not missing at random' by conducting ITT analyses. However, this might result in an too optimistic assessment of incidences. Therefore, conducted analyses in the review were PP. As pre-described, we conducted sensitivity analyses according to best and worst case scenarios to gain information on the impact of missing data.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Coronary Syndrome [psychology]; Antidepressive Agents [*therapeutic use]; Bias; Brain Injuries, Traumatic [psychology]; Breast Neoplasms [psychology]; Depression [epidemiology] [*prevention & control]; Head and Neck Neoplasms [psychology]; Incidence; Macular Degeneration [psychology]; Primary Prevention [*methods]; *Problem Solving; Randomized Controlled Trials as Topic; Stroke [psychology]; Tertiary Prevention [*methods]

MeSH check words

Female; Humans; Male