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Antidepressants for the treatment of depression in people with cancer (Review)

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[Intervention Review]

Antidepressants for the treatment of depression in people with cancer

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ABSTRACT

Background

Major depression and other depressive conditions are common in people with cancer. These conditions are not easily detectable in clinical practice, due to the overlap between medical and psychiatric symptoms, as described by diagnostic manuals such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases (ICD). Moreover, it is particularly challenging to distinguish between pathological and normal reactions to such a severe illness. Depressive symptoms, even in subthreshold manifestations, have been shown to have a negative impact in terms of quality of life, compliance with anti-cancer treatment, suicide risk and likely even the mortality rate for the cancer itself. Randomised controlled trials (RCTs) on the efficacy and tolerability of antidepressants in this population group are few and often report conflicting results.

Objectives

To assess the effects and acceptability of antidepressants for treating depressive symptoms in adults (18 years or older) with cancer (any site and stage).

Search methods

We searched the following electronic bibliographic databases: the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 3), MEDLINE Ovid (1946 to April week 3, 2014), EMBASE Ovid (1980 to 2014 week 17) and PsycINFO Ovid (1987 to April week 4, 2014). We additionally handsearched the trial databases of the most relevant national, international and pharmaceutical company trial registers and drug-approving agencies for published, unpublished and ongoing controlled trials.

Selection criteria

We included RCTs allocating adults (18 years or above) with any primary diagnosis of cancer and depression (including major depressive disorder, adjustment disorder, dysthymic disorder or depressive symptoms in the absence of a formal diagnosis) comparing antidepressants versus placebo, or antidepressants versus other antidepressants.

Data collection and analysis

Two review authors independently checked eligibility and extracted data using a form specifically designed for the aims of this review. The two authors compared the data extracted and then entered data into RevMan 5 with a double-entry procedure. Information extracted included study and participant characteristics, intervention details, outcome measures for each time point of interest, cost analysis and sponsorship by a drug company. We used the standard methodological procedures expected by The Cochrane Collaboration.

Main results

We retrieved a total of nine studies (861 participants), with seven studies contributing to the meta-analysis for the primary outcome. Four of these compared antidepressants and placebo, two compared two antidepressants and one-three armed study compared two antidepressants and a placebo arm. For the acute phase treatment response (6 to 12 weeks), we found very low quality evidence for the effect of antidepressants as a class on symptoms of depression compared with placebo when measured as a continuous outcome (standardised mean difference (SMD) -0.45, 95% confidence interval (CI) -1.01 to 0.11, five RCTs, 266 participants) or as a proportion of people who had depression (risk ratio (RR) 0.82, 95% CI 0.62 to 1.08, five RCTs, 417 participants). No trials reported data on the follow-up response (more than 12 weeks). In head-to-head comparisons we only retrieved data for selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants, providing very low quality evidence for the difference between these two classes (SMD -0.08, 95% CI -0.34 to 0.18, three RCTs, 237 participants). No clear evidence of an effect of antidepressants versus either placebo or other antidepressants emerged from the analyses of the secondary efficacy outcomes (dichotomous outcome, response at 6 to 12 weeks, very low quality evidence). We found very low quality evidence for the effect of antidepressants as a class in terms of dropouts due to any cause compared with placebo (RR 0.87, 95% CI 0.49 to 1.53, six RCTs, 455 participants), as well as between SSRIs and tricyclic antidepressants (RR 0.83, 95% CI 0.53 to 1.30, three RCTs, 237 participants). We downgraded the quality of the evidence because the included studies were at an unclear or high risk of bias due to poor reporting, imprecision arising from small sample sizes and wide confidence intervals, and inconsistency due to statistical or clinical heterogeneity.

Authors' conclusions

Despite the impact of depression on people with cancer, available studies were very few and of low quality. This review found very low quality evidence for the effects of these drugs compared with placebo. On the basis of these results clear implications for practice cannot be made. The use of antidepressants in people with cancer should be considered on an individual basis and, considering the lack of head-to-head data, the choice of which agent should be prescribed may be based on the data on antidepressant efficacy in the general population of individuals with major depression, also taking into account that data on medically ill patients suggest a positive safety profile for the SSRIs. Large, simple, randomised, pragmatic trials comparing commonly used antidepressants versus placebo in people with cancer with depressive symptoms, with or without a formal diagnosis of a depressive disorder, are urgently needed to better inform clinical practice.

PLAIN LANGUAGE SUMMARY

Antidepressants for the treatment of depression in people with cancer

The issue:

Depressive states are frequent complications among people suffering from cancer. Often depressive symptoms are a normal reaction or a direct effect of such a severe and life-threatening illness. It is therefore not easy to establish when depressive symptoms become a proper disorder and need to be treated with drugs. Current scientific literature reveals that depressive symptoms, even when mild, can have a relevant impact on the course of cancer, reducing the overall quality of life and affecting compliance with anti-cancer treatment, as well as possibly increasing the cancer mortality rate.

The aim of the review:

It is therefore important to assess the possible beneficial role of antidepressants in adults (18 years or above) with cancer. The aim of the review is to assess the efficacy and acceptability of antidepressants for treating depressive symptoms in patients with cancer at any site and stage.

What are the main findings?

We systematically reviewed nine studies assessing the efficacy of antidepressants, for a total of 861 participants. Due to the small number of people in the studies and issues with the reporting about how the studies were done there is uncertainty over whether antidepressants

were better than placebo in terms of depressive symptoms after 6 to 12 weeks of treatment. We did not have enough evidence to determine how well antidepressants were tolerated in comparison with placebo. Our results could not show whether any antidepressant was better than any other in terms of both beneficial and harmful effects. Large randomised studies are still needed to better inform clinical practice. We cannot draw reliable conclusions about the effects of antidepressants on depression in people with cancer.

Quality of the evidence:

The quality of the evidence was very low because of a lack of information about how the studies were designed, low numbers of people in the analysis of results, and differences between the characteristics of the studies and their results.

What are the conclusions?

Despite the impact of depression on people with cancer, available studies were very few and of low quality. This review found very low quality evidence for the effects of these drugs compared with placebo.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antidepressants compared to placebo for patients with cancer and depression

Patient or population: patients with cancer and depression
Settings: in- and outpatients
Intervention: antidepressants
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Antidepressants				
Efficacy as a continuous outcome Follow-up: 6 to 12 weeks		The mean efficacy as a continuous outcome (SMD) in the intervention groups was **0.45 standard deviations lower** (1.01 lower to 1.11 higher)		266 (5 studies, 6 comparisons)	⊕○○○ **very low**[1,2,3,4]	
Efficacy as a dichotomous outcome Follow-up: 6 to 12 weeks	**358 per 1000**	**294 per 1000** (222 to 387)	**RR 0.82** (0.62 to 1.08)	417 (5 studies, 6 comparisons)	⊕○○○ **very low**[1,3,4,5]	
Acceptability - dropouts due to any cause Follow-up: 4 to 12 weeks	**215 per 1000**	**187 per 1000** (105 to 328)	**RR 0.87** (0.49 to 1.53)	455 (6 studies, 7 comparisons)	⊕○○○ **very low**[1,3,4,6]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No studies described the outcome assessment as masked. This should be considered a major limitation, which is likely to result in a biased assessment of the intervention effect.
[2]I^2 = 77%, which indicates a serious risk of inconsistency (unexplained heterogeneity).
[3]Very low number of participants recruited (fewer than 100 individuals in both treatment arms) and 95% CI includes both no effect and appreciable benefit or appreciable harm, which suggests the risk of very serious imprecision of the results and thus low confidence in their reliability.
[4]Two out of five studies had a high risk of sponsorship bias.
[5]I^2 = 49%. An I^2 between 50% and 75% suggests a serious risk of inconsistency, which may arise from relevant differences in populations, interventions and outcomes of the studies entered into the analysis.
[6]I^2 = 53%. See above.

BACKGROUND

Description of the condition

The prevalence of major depression among people with cancer has been estimated to be around 15% in oncological and haematological settings, with similar rates in palliative care settings. Adding other depressive diagnoses, including dysthymia and minor depression, prevalence rates rise up to 20% in oncological and haematological settings, and up to 25% in palliative care settings (Mitchell 2011).

Formulating a diagnosis of depression in patients affected by serious medical conditions is particularly challenging, as several symptoms of the medical condition may overlap with those described in the Diagnostic and Statistical Manual (DSM) (APA 1994) and the International Classification of Diseases (ICD) (WHO 1992) for depression, such as fatigue, weight loss and sleep disturbances. Furthermore, besides physical symptoms, cancer progression is associated with functional, social and relational impairment. Even recurrent thoughts of death might be a normal reaction to a limited life expectancy or to severe pain syndromes. It has recently been reported that atypical depressive symptoms, such as anxiety, despair, inner restlessness and social withdrawal might be more frequent in this population, and need to be taken into account when depressive symptoms are assessed (Brenne 2013).

Cancer may increase patients' susceptibility to depression in several ways. First, a reaction to a severe diagnosis and the forthcoming deterioration of health status may constitute a risk factor for depression; second, treatment with immune response modifiers and chemotherapy regimens, as well as metabolic and endocrine alterations, chronic pain and extensive surgical interventions, may represent additional contributing factors (Irwin 2013; Onitilo 2006). In people with cancer, depression and other psychiatric comorbidities are responsible for a worsened quality of life (Arrieta 2013), lower compliance with anti-cancer treatment (Colleoni 2000), prolonged hospitalisation (Prieto 2002), higher suicide risk (Shim 2012), and greater psychological burden on the family (Kim 2010). Furthermore, depression is likely to be an independent risk factor for cancer mortality (Lloyd-Williams 2009; Pinquart 2010), with estimates as high as a 26% greater mortality rate among patients with depressive symptoms and a 39% higher mortality rate among those with a diagnosis of major depression (Satin 2009). The effects of depression on mortality may differ by cancer site, being highest in people with lung and gastrointestinal cancer, and lower in those with genitourinary and skin cancer (Onitilo 2006). However, data are sparse and conflicting on this compelling issue (Pinquart 2010). As a consequence individuals with cancer, major depression and depressive symptoms may have radically different features compared with individuals without cancer in terms of underlying risk factors, natural history, outcome and antidepressant treatment response (Brenne 2013; Irwin 2013).

Description of the intervention

Antidepressants are the most common psychotropic drugs prescribed in people with depression. Amongst antidepressants, many different agents are available, including tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and other newer agents, such as agomelatine, mirtazapine, reboxetine and bupropion. It has been repeatedly shown that SSRIs are not more effective than TCAs (Anderson 2000; Mottram 2009), but are better tolerated and safer in overdose than TCAs (Anderson 2000; Barbui 2001; Henry 1995).

In a narrative review covering pharmacological, psychological and psychosocial interventions, Li 2012 reported controversial findings on the effectiveness of antidepressants for the prevention and treatment of depressive symptoms in people with cancer. There were few available trials and the findings were not consistent. It has been suggested that in people with cancer, CANMAT level I evidence (at least two randomised controlled trials (RCTs) with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals (CIs)) is available only for mianserin for the treatment of depressive symptoms and for paroxetine for the prevention of new episodes (Li 2012). A meta-analysis of the efficacy of psychological and pharmacological interventions by Hart 2012 identified only four eligible trials assessing the efficacy of antidepressant drugs. A more recent meta-analysis, carried out by Laoutidis 2013, found six placebo-controlled trials and three head-to-head trials concerning the treatment of depression in people with cancer at any stage and site. Among these trials, substantial heterogeneity was found (i.e. relevant variability of participants, interventions and outcome due to different clinical, methodological and statistical approaches) (Higgins 2011). The meta-analysis showed an improvement in depressive symptoms in patients treated with antidepressants with an overall risk ratio of 1.56 (95% confidence interval (CI) 1.07 to 2.28). No difference in dropouts was found between groups. Subgroup analysis failed to identify differences between TCAs and SSRIs, and found that subsyndromal depressive symptoms (i.e. symptoms which do not reach the status of a formal depressive syndrome as it is described by diagnostic manuals, such as DSM or ICD) may similarly improve with antidepressant treatment (Laoutidis 2013). Similar findings have been previously shown in physically ill people in a meta-analytic study (Rayner 2010).

A meta-analysis by Walker 2014, which included trials carried out in people with a formal diagnosis of depression, found limited evidence in favour of the use of antidepressant drugs. However, only two placebo-controlled trials were included, and in both of them the antidepressant was mianserin, an agent rarely used in current clinical practice. More recently Riblet and colleagues (Riblet 2014), who systematically reviewed the evidence comparing antidepressants and placebo in individuals with any type and stage of cancer and comorbid depression of any severity, retrieved 10 trials suitable for a meta-analysis on the efficacy of antidepressant. They

concluded that fluoxetine, paroxetine and mianserin may improve cancer-related depression. However, one quasi-randomised trial was included and two trials included patients who were not depressed at baseline.

Rayner 2011a conducted a meta-analytic study on the efficacy of antidepressants in people receiving palliative care (including cancer and several other life-threatening illnesses) and suffering from depression (including major depressive disorder, adjustment disorder and dysthymic disorder based on standardised criteria, and/or according to a score above a certain cut-off on validated tools). This review detected a beneficial effect associated with antidepressant treatment and suggested that in people in palliative care milder depressive disorders, as well as major depression, may be responsive to antidepressant treatment. These findings were incorporated into European guidelines on the management of depression in palliative cancer care (Rayner 2011b), in which use of an antidepressant is recommended, not only in major depression but also in mild depression, if symptoms persist after first-line treatments have failed (including assessment of the quality of relationships with significant others, psychosocial support, guided self help programmes and brief psychological interventions). However, there is still a lack of evidence as to whether antidepressants are all similarly effective in this population.

How the intervention might work

Antidepressants are a heterogeneous class of drugs, in which a common mechanism of action is not traceable. Their therapeutic action may be related to their ability to affect serotonin, norepinephrine and dopamine neurotransmission systems, according to the broadly studied theory about monoamine dysregulation as the key neurophysiological event underlying mood disorders. However, in recent years, alternative mechanisms have been shown, making progressively clearer the complexity of interactions between several systems on which the action of these drugs rely. For instance, current research on new antidepressant drugs focuses on affecting mechanisms related to glutamate (Lapidus 2013) and melatonin transmission (Hickie 2011), neural proliferation and plasticity in limbic areas (Pilar-Cuéllar 2013), and endocrine system activities (hypothalamic-pituitary-adrenal axis in particular) (Sarubin 2014), as well as antioxidant, anti-inflammatory and immunologic pathways (Lopresti 2012).

The extent to which each of these components can contribute to the dysregulation of the brain's homeostatic system could vary extensively among different individuals, according also with several biological, environmental and psychological factors (Shelton 2007). For this reason, even if the efficacy of antidepressants has been proven for some kinds of depressive conditions, we cannot assume these data to be reliable in the same way for people with cancer, for whom several further factors may be involved in the pathogenesis (including psychological, immunologic and metabolic factors, as well as pain and highly distressing treatments).

In most cases antidepressant dose should be gradually titrated and treatment effect takes usually some weeks to show up. Antidepressants may require adjustment over time to ensure an appropriate dose is given. Moreover, it has been highlighted that compliance represents a relevant factor for an antidepressant's efficacy (Vergouwen 2003).

Why it is important to do this review

Providing better interventions to people suffering from cancer and depressive symptoms is an important goal. While Cochrane reviews are available on the efficacy of psychotherapy (Akechi 2008) and psychosocial interventions (Galway 2012), no Cochrane review has been performed on the efficacy of antidepressants in this patient population.

Laoutidis 2013 included participants with depressive disorder and subsyndromal depressive symptoms, identified nine randomised trials and showed antidepressants to be superior to placebo. In their review, however, only trials in English were included, unpublished trials were not sought and trials with depression as a secondary outcome were excluded. Further, the authors performed a meta-analysis on dichotomous data only.

Considering these limitations and that available systematic reviews provide contrasting findings (Hart 2012; Laoutidis 2013; Li 2012; Rodin 2007), there is still uncertainty as to the true efficacy of antidepressants (Rooney 2010; Rooney 2013; Walker 2014). Moreover, most of the previous reviews focused on elevated depressive symptoms (Hart 2012), or major depression (Iovieno 2011; Ng 2011; Walker 2014), while current findings suggest that depressive symptoms, even in subsyndromal manifestations, could represent an independent risk factor for the burden of disease (Arrieta 2013; Brenne 2013; Pinquart 2010; Satin 2009). Although the efficacy of antidepressants in minor depression, dysthymia and adjustment disorder is still not clear (Barbui 2011; Casey 2011; Silva de Lima 1999; Silva de Lima 2005), different authors suggest that antidepressants are effective in people suffering from severe medical illness (including cancer), even for subthreshold depressive symptoms (Laoutidis 2013; Rayner 2010; Rayner 2011a).

OBJECTIVES

To assess the effects and acceptability of antidepressants for treating depressive symptoms in adults (18 years or older) with cancer (any site and stage).

METHODS

Criteria for considering studies for this review

Types of studies

We only included randomised controlled trials (RCTs). We excluded trials using quasi-random methods. We included trials published in any language.

Types of participants

We included adults (18 years or older) with any primary diagnosis of cancer (confirmed with appropriate clinical and instrumental assessment) and major depressive disorder, adjustment disorder, dysthymic disorder or depressive symptoms in the absence of a formal diagnosis of major depression. We included participants receiving antidepressants for other indications (e.g. fatigue, neuropathic pain, hot flushes, etc.) only if the criterion of being affected by one of the above-mentioned depressive conditions was met at the time of enrolment.

For trials including a diagnosis of depression, we included any standardised criteria. Most recent trials use DSM-IV (APA 1994), or ICD-10 (WHO 1992) criteria. Older trials use ICD-9 (WHO 1978), DSM-III (APA 1980)/DSM- III-R (APA 1987), or other diagnostic systems. For trials including depressive symptoms in the absence of a formal diagnosis of major depression, we only included those employing standardised criteria to measure depressive symptoms and with evidence of adequate validity and reliability. Most recent trials use the Hamilton Rating Scale for Depression (HRSD) (Hamilton 1960), the Beck Depression Inventory (BDI) (Beck 1961), the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), or the Hospital Anxiety and Depression Scale (HADS) (Zigmond 1983).

Types of interventions

We included the following antidepressants, reported in the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Index (updated to August 2013) from the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology website (http://www.whocc.no):

- non-selective monoamine reuptake inhibitors, such as amitriptyline, desipramine, imipramine, imipramine oxide, nortriptyline, clomipramine, dosulepin, doxepin, opipramol, trimipramine, lofepramine, dibenzepin, protriptyline, iprindole, melitracen, butriptyline, amoxapine, dimetacrine, amineptine, maprotiline, quinupramine;
- selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, sertraline, alaproclate, etoperidone, zimeldine;
- monoamine oxidase A inhibitors, such as moclobemide, toloxatone;
- non-selective monoamine oxidase inhibitors, such as isocarboxazid, nialamide, phenelzine, tranylcypromine, iproniazide, iproclozide;
- any newer antidepressant and any other non-conventional antidepressive agents, such as mianserin, trazodone, nefazodone, mirtazapine, bupropion, venlafaxine, desvenlafaxine, duloxetine, reboxetine, agomelatine, milnacipran, oxitriptan, tryptophan, nomifensine, minaprine, bifemelane, viloxazine, oxaflozane, medifoxamine, tianeptine, pivagabine, gepirone, vilazodone, Hyperici herba.

The comparison group was placebo and/or any other antidepressants (head-to-head comparisons).

We excluded trials in which antidepressants were compared with another type of psychopharmacological agent, i.e. psycho-stimulants, anxiolytics, anticonvulsants, antipsychotics or mood stabilisers.

Types of outcome measures

Primary outcomes

Efficacy as a continuous outcome

We extracted and analysed group mean scores at different time points and, if these were not available, group mean change scores, on the Hamilton Rating Scale for Depression (HRSD), Montgomery and Åsberg Depression Rating Scale (MADRS) or Clinical Global Impression Rating scale (CGI), or on any other depression rating scale with evidence of adequate validity and reliability, as follows:

- early response: between one and four weeks, giving preference to the time point closest to two weeks;
- acute phase treatment response: between 6 and 12 weeks, giving preference to the time point given in the original trial as the study endpoint;
- follow-up response: after 12 weeks, giving preference to the time point closest to 24 weeks.

The acute phase treatment response (between 6 and 12 weeks) was our primary outcome of interest.

Secondary outcomes

Efficacy as a dichotomous outcome

Treatment responders during the 'acute phase' (between 6 and 12 weeks): proportion of participants showing a reduction of at least 50% on the HRSD or MADRS or any other depression scale (e.g. the Beck Depression Inventory (BDI) or the Center for Epidemiologic Studies Depression Scale (CES-D)), or who were 'much or very much improved' (score 1 or 2) on the Clinical Global Impression-Improvement (CGI-I) scale, or the proportion of participants who improved using any other pre-specified criterion.

Social adjustment

Mean scores on social adjustment rating scales (e.g. Global Assessment of Functioning - GAF), as defined by each of the trials, during the 'acute phase' (between 6 and 12 weeks),

Health-related quality of life

Mean scores on quality of life (QoL) rating scales during the 'acute phase' (between 6 and 12 weeks). We gave preference to illness-specific QoL measures, such as the European Organisation for Research and Treatment into Cancer Quality of Life Questionnaire-30 (EORTC QLQ-30) (Aaronson 1993), the Functional Assessment of Cancer Therapy (FACT) scale (Cella 1993), and the Short Form (36) Health Survey (SF-36) (Ware 1980; Ware 1992). When such tools were not employed, we used a general health-related QoL measure with evidence of adequate validity and reliability, as defined by each of the trials.

Acceptability (dropouts)

- number of participants who dropped out during the trial as a proportion of the total number randomised (total dropout rate);
- number of participants who dropped out due to inefficacy during the trial as a proportion of the total number randomised (dropout rates due to inefficacy);
- number of participants who dropped out due to adverse effects during the trial as a proportion of the total number randomised (dropout rates due to adverse effects).

We extracted acceptability outcomes at trial endpoint only.

Search methods for identification of studies

Electronic searches

We searched the following electronic bibliographic databases: the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 3) (Appendix 1), MEDLINE Ovid (1946 to April week 3 2014) (Appendix 2), EMBASE Ovid) (1980 to 2014 week 17) (Appendix 3) and PsycINFO Ovid (1987 to April week 4 2014) (Appendix 4).

Searching other resources

Handsearches

We handsearched the trial databases of the following drug-approving agencies for published, unpublished and ongoing controlled trials: the Food and Drug Administration (FDA) in the United States (http://www.fda.gov), the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (http://www.mhra.gov.uk/), the European Medicines Agency (EMA) in the European Union (http://www.ema.europa.eu), the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan (http://www.pmda.go.jp/english/) and the Therapeutic Goods Administration (TGA) in Australia (http://www.tga.gov.au/).

We additionally searched the following trial registers: clinicaltrials.gov in the United States (http://clinicaltrials.gov/), ISRCTN and National Research Register in the United Kingdom (http://www.controlled-trials.com/), UMIN-CTR in Japan (http://www.umin.ac.jp/ctr/), the ANZ-CTR in Australia and New Zealand (http://www.anzctr.org.au/), the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) and the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Clinical Trials Portal (http://clinicaltrials.ifpma.org/clinicaltrials).

We also handsearched appropriate journals and conference proceedings relating to depression treatment in people with cancer. We also handsearched the websites of the most relevant pharmaceutical companies producing antidepressants, such as GlaxoSmithKline (http://www.gsk-clinicalstudyregister.com/), Sanofi (http://en.sanofi.com/rd/clinical_trials), Janssen (http://www.janssenrnd.com/our-innovation/clinical-trails), Lundbeck (http://www.lundbeck.com/trials), Pfizer (http://www.pfizer.co.uk/content/clinical-trials), Abbott (http://www.abbott.com/abbott-citizenship.html), Lilly (http://www.lillytrials.com/), and Merck (http://www.merck.com/research/discovery-and-development/clinical-development/home.html) for published, unpublished and ongoing controlled trials.

We also searched reference lists of included trials and other relevant studies.

Personal communication

We searched the websites of pharmaceutical companies (list reported in the methods) and contacted the authors of the unpublished studies. Only one author provided data from one unpublished study.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to a reference management database (Endnote) and removed duplicates. Two review authors (GO and FM) examined the remaining references independently. We excluded those trials that clearly did not meet the inclusion criteria, and we obtained copies of the full text of potentially relevant references. Two review authors (GO and FM) independently assessed the eligibility of retrieved trials. Disagreements were resolved by discussion between

the two review authors and, if necessary, with a third review author (CB). We documented reasons for exclusion. We nested multiple reports of the same trials to ensure that no data were included in the meta-analysis more than once.

Data extraction and management

Two review authors (GO and FM), working independently and in duplicate, extracted data from the included trials using a data collection sheet (see Appendix 5), which was developed in accordance with recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; chapter 7). If the trial was a three (or more)-armed trial involving a placebo arm, we also extracted data from the placebo arm.

Data included:

- first author, year and journal;
- methodological features (study design, randomisation, blinding and allocation concealment, follow-up period);
- participant characteristics (gender, age, study setting, number of participants randomised to each arm, depression diagnosis, previous history of depression, cancer site and stage, cancer treatment);
- intervention details (antidepressant and other interventions employed, dosage range, mean daily dosage prescribed);
- outcome measures for each time point of interest. Continuous measures encompassed mean scores of rating scales, standard deviation or standard error; dichotomous measures were endpoint response rate and dropout rate, which were calculated on a strict intention-to-treat (ITT) basis;
- cost analysis (estimates of the cost of resources employed to perform the trial);
- presence of sponsorship by a drug company.

Alongside the data which contributed to meta-analysis, we collected characteristics of participants, settings, interventions and methodological approaches, in order to provide an overall view of the available evidence on this topic (see Description of studies), as well as to perform an accurate assessment of the risk of bias (see Risk of bias in included studies). These elements provided a crucial contribution to the discussion, with particular regards to the clinical applicability of the results of the study (see Overall completeness and applicability of evidence; Implications for practice).

Assessment of risk of bias in included studies

Two review authors (GO and FM) independently assessed the risk of bias of all included trials in accordance with The Cochrane Collaboration's tool in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which includes the following assessments: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (detection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting of outcomes (reporting bias) and other biases (e.g. sponsorship bias). To determine the risk of bias of a trial, for each criterion we evaluated the presence of sufficient information and the likelihood of potential bias. We rated each criterion as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias' (indicating either lack of information or uncertainty over the potential for bias). Particular attention was given to the adequacy of the random allocation concealment and blinding of participants, personnel and outcome assessors. If inadequate details of methodological characteristics of trials were provided, we contacted the authors in order to obtain further information. If the raters disagreed, the final rating was made by consensus with the involvement (if necessary) of a third review author (CB). We summarised results in a 'Risk of bias' graph and a 'Risk of bias' summary and discussed and interpreted the results of meta-analysis win light of the findings and with respect to the risk of bias.

Measures of treatment effect

1. Continuous data

We evaluated the efficacy of treatments as a continuous measure, namely the group mean scores on depression rating scales at the acute phase (between 6 and 12 weeks). We employed other continuous data for some secondary outcomes, namely efficacy at early response (between one and four weeks), efficacy at follow-up response (after 12 weeks), social adjustment and health-related quality of life.

2. Dichotomous data

We employed dichotomous data for some secondary outcomes, namely the efficacy as the number of treatment responders at the acute phase (between 6 and 12 weeks) and the acceptability as the proportion of dropouts.

Unit of analysis issues

1. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, on entry to the second phase, the participants can differ systematically from their initial state, even despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). Both effects are very likely in major depression, thus we planned to use only data from the first phase of cross-over trials.

2. Cluster-randomised trials

We planned to use the generic inverse variance technique to appropriately analyse cluster-randomised trials, taking into account intra-class correlation coefficients to adjust for cluster effects.

Dealing with missing data

At some degree of loss to follow-up, data must lose credibility (Xia 2009). For any particular outcome, if more than 50% of data were unaccounted for, we did not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a trial were lost, but the total loss was less than 50%, we planned to mark such data with (*) to indicate that such a result may be prone to bias. When dichotomous or continuous outcomes were not reported, we asked trial authors to supply the data.

We calculated dichotomous data on a strict intention-to-treat (ITT) basis: dropouts were always included in this analysis. Where participants have been excluded from the trial before the endpoint, we assumed that they experienced a negative outcome by the end of the trial. For continuous variables, we applied a loose ITT analysis, whereby all the participants with at least one post-baseline measurement were represented by their last observations carried forward (LOCF), with due consideration of potential biases, including number and timings of dropouts in each arm.

When relevant outcomes were not reported, we asked trial authors to supply the data. In the absence of data from authors, we only employed validated statistical methods to impute missing outcomes, with due consideration of the possible bias of these procedures, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and with www.missingdata.org.uk.

When standard deviations (SDs) were not reported, we asked authors to supply the data. When only the standard error (SE) or t-statistics or P values were reported, we calculated SDs according to Altman 1996. In the absence of data from the authors, we substituted SDs with those reported in other trials in the review (Furukawa 2006).

Assessment of heterogeneity

We investigated heterogeneity between trials using the I^2 statistic (Higgins 2003; Ioannidis 2008) (we considered an I^2 value equal to or more than 50% to indicate substantial heterogeneity) and by visual inspection of the forest plots.

Assessment of reporting biases

We had planned to use the tests for funnel plot asymmetry to investigate small-study effects (Sterne 2000), if there were at least 10 trials included in the meta-analysis, with cautious interpretation of the results by visual inspection (Higgins 2011). Since no analysis with at least 10 trials was included we did not use a funnel plot. When evidence of small-study effects was identified, we aimed to investigate possible reasons for funnel plot asymmetry, including publication bias.

Data synthesis

If a sufficient number of clinically similar studies was available, we pooled their results in meta-analyses.

For continuous data we pooled the mean differences (MDs) with a 95% confidence interval (CI) between the treatment arms at the time point of interest, if all trials measured the outcome using the same rating scale, otherwise we pooled standardised mean differences (SMDs). For dichotomous data, we pooled the risk ratio (RR) with a 95% CI. For the analysis of dichotomous data we employed the Mantel-Haenszel methods. For statistically significant results, we calculated the number needed to treat to provide benefit (NNTB). We included trials that compared more than two intervention groups of the same drug (i.e. different dosages) in meta-analysis by combining arms of the trials into a single group, for the intervention and for the control group respectively, as recommended in section 16.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If data were binary, we simply added and combined them into one group or divided the comparison arm into two (or more) as appropriate. If data were continuous, we combined the data following the formula in Chapter 7, section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We included trials that compared two or more antidepressants with placebo as independent comparisons, splitting the 'shared' group (placebo) into two or more groups with smaller sample size (Higgins 2011).

We chose a random-effects model as heterogeneity was expected (Higgins 2011). We only considered direct comparisons for the meta-analysis.

Subgroup analysis and investigation of heterogeneity

We aimed to perform the following subgroup analyses for the primary outcome:

- psychiatric diagnosis, separating major depressive disorder, and pooling data from studies including only participants with adjustment disorder, dysthymic disorder, depressive symptoms;
- previous history of depressive conditions;
- antidepressant class, in particular separating SSRIs, TCAs and other antidepressants;
- cancer site, separating breast cancer and other sites;
- cancer stage, separating early stages (stage 0 and I) and late stages (stage II, III and IV);
- gender.

We interpreted subgroup analyses with caution, as multiple analyses can lead to false positive conclusions (Oxman 1992).

Sensitivity analysis

We aimed to perform the following sensitivity analyses for the primary outcome:

1. excluding trials in which the randomisation process was not clearly reported;
2. excluding trials with unclear concealment of random allocation;
3. excluding trials that did not employ adequate blinding of participants, healthcare providers and outcome assessors;
4. excluding trials that did not employ depressive symptoms as their primary outcome;
5. excluding trials with imputed data.

'Summary of findings' table

We prepared the 'Summary of findings' tables, summarising the key findings of the systematic review in line with the standard methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). These findings include:

1. antidepressants compared to placebo for depressive symptoms in people with cancer;
   i) efficacy as a continuous outcome;
   ii) efficacy as a dichotomous outcome;
   iii) acceptability (dropouts).
2. antidepressants compared to other antidepressants for depressive symptoms in people with cancer;
   i) efficacy as a continuous outcome;
   ii) efficacy as a dichotomous outcome;
   iii) acceptability (dropouts).

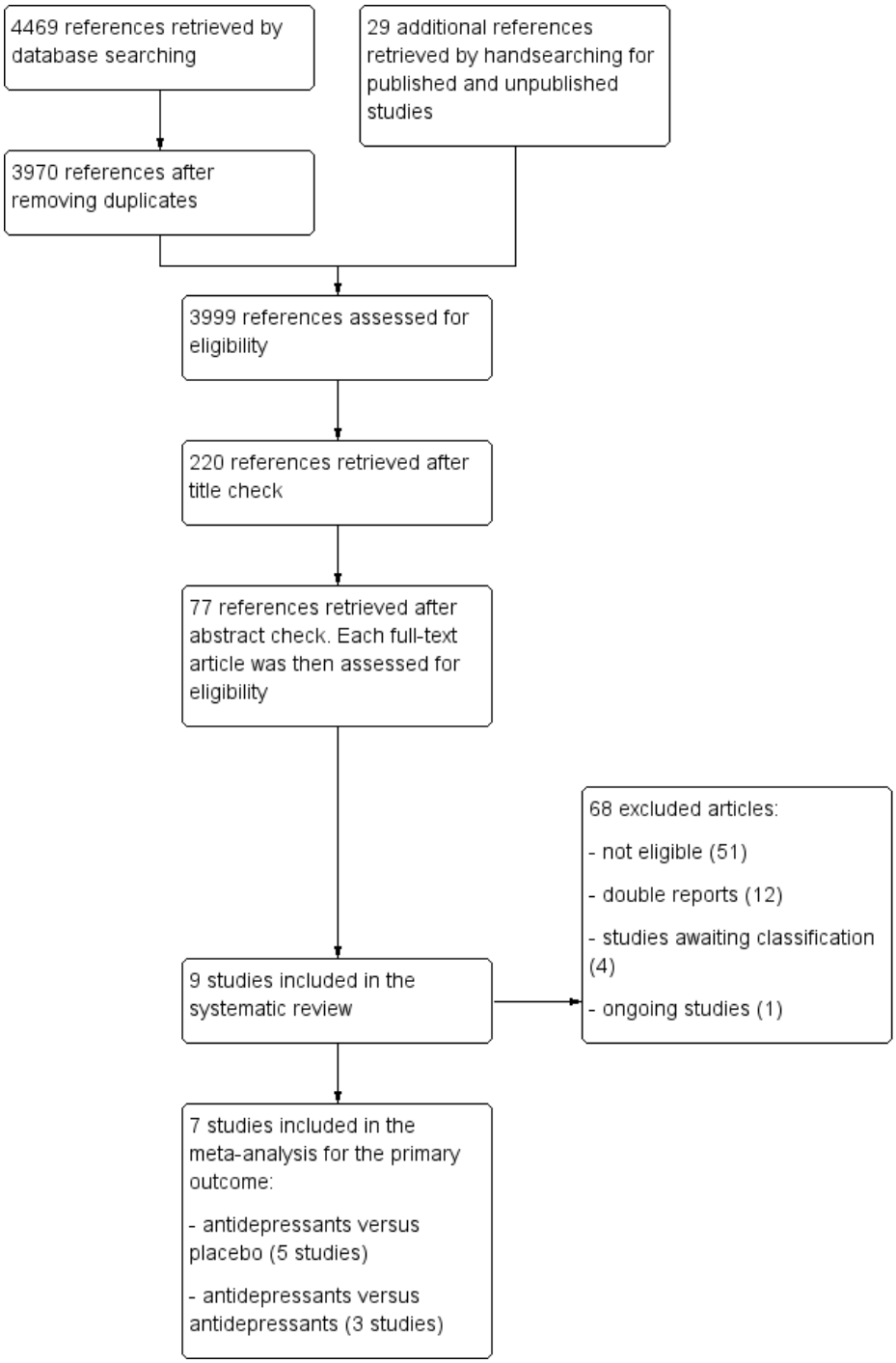
RESULTS

Description of studies

Results of the search

Figure 1 illustrates the process of study selection. The search of the electronic databases retrieved 4469 references. After eliminating the duplicates, we identified 3970 references for screening. We added 29 further references from the handsearching of articles' references and the websites of drug-approving agencies' and pharmaceutical companies. Two review authors (GO, FM) independently checked 10% of the titles. Since the degree of agreement was 'good' according to the *Cochrane Handbook for Systematic Reviews of Interventions* (simple kappa statistic 0.73), one review author (GO) checked the remaining titles. From the 220 titles identified, the two review authors independently checked 50% of the abstracts. The degree of agreement was 'fair' according to the *Cochrane Handbook for Systematic Reviews of Interventions* (simple kappa statistic 0.41). The two review authors discussed the abstracts for which there was inconsistency between them and achieved a complete agreement. One review author (GO) checked the remaining abstracts. The two review authors examined the full text of all of the 77 studies identified after the abstract check in detail. Nine studies fulfilled the criteria for eligibility and were included in the review (Costa 1985; EUCTR2008-002159-25-FR; Fisch 2003; Holland 1998; Musselman 2006; Navari 2008; Pezzella 2001; Razavi 1996; Van Heeringen 1996). Only seven studies contributed to the meta-analysis for the primary outcome (EUCTR2008-002159-25-FR; Fisch 2003; Holland 1998; Musselman 2006; Pezzella 2001; Razavi 1996; Van Heeringen 1996). Costa 1985 contributed only to the meta-analysis for secondary outcomes and Navari 2008 did not provide useful data for the meta-analysis.

Figure 1. Flow diagram.



Included studies

Overall, a total of nine studies were included - eight published studies (Costa 1985; Fisch 2003; Holland 1998; Musselman 2006; Navari 2008; Pezzella 2001; Razavi 1996; Van Heeringen 1996), and one unpublished study (EUCTR2008-002159-25-FR). A total of 861 participants were involved in these studies. A detailed description of each study is reported in the section Characteristics of included studies.

Design and interventions

All the included studies were reported to be randomised and double-blind. The participants were followed up for six weeks in three trials, 24 weeks in one trial and for a mean of 15 weeks in one trial (range between 4 and 24 weeks). Six studies had two arms and explored the efficacy of an antidepressant versus placebo (Costa 1985; EUCTR2008-002159-25-FR; Fisch 2003; Navari 2008; Razavi 1996; Van Heeringen 1996). In four of these studies the antidepressants was fluoxetine, an SSRI (EUCTR2008-002159-25-FR; Fisch 2003; Navari 2008; Razavi 1996), and in two the tetracyclic antidepressant mianserin was evaluated (Costa 1985; Van Heeringen 1996). Two studies compared two antidepressants with a two-arm, head-to-head study design (paroxetine versus amitriptyline and fluoxetine versus desipramine respectively) (Holland 1998, Pezzella 2001). One study used a three-arm design, comparing paroxetine versus desipramine versus placebo (Musselman 2006). In these three studies the head-to-head comparisons were between a tricyclic antidepressant and a SSRI.

Sample sizes

The mean number of participants per study was approximately 96, with a minimum sample size of 35 (Musselman 2006), and a maximum of 193 (Navari 2008). Only three studies had more than 100 participants (Fisch 2003; Navari 2008; Pezzella 2001).

Setting

Four of nine trials enrolled only outpatients (Fisch 2003; Musselman 2006; Navari 2008; Van Heeringen 1996). Inpatients and outpatients were enrolled in one trial (Costa 1985). For the remaining four trials the setting was not clearly reported (EUCTR2008-002159-25-FR; Holland 1998; Pezzella 2001; Razavi 1996).

Participants

Two trials excluded people over 65 years (Holland 1998; Van Heeringen 1996), while no trials included only elderly participants.The population of participants was heterogeneous in terms of diagnosis of depression. Two trials enrolled only participants with a diagnosis of major depression based on DSM-III in association with a score greater than 16 on the 21-item HRSD (Hamilton Rating Scale for Depression) (Van Heeringen 1996), or only on ICD-10 criteria (Pezzella 2001). Three studies enrolled both people with a diagnosis of major depression and people with adjustment disorders based on DSM-III-R (Holland 1998), on DSM-III-R in association with a score greater than 14 on the first 17 items of the 21-item HRSD (Musselman 2006), or on DSM-III-R in association with a score greater than 13 on the HADS (Hospital Anxiety and Depression Scale) (Razavi 1996). However, in the Musselman 2006 trial only people with major depression took part in the study. Three studies enrolled people with depressive symptoms, but without a formal diagnosis of depression according to a cut-off score on standardised rating scales, respectively TQSS (Two-Question Screening Survey) greater than 2 (Fisch 2003; Navari 2008) and HADS (Hospital Anxiety and Depression Scale) greater than 11 (EUCTR2008-002159-25-FR). Costa 1985 used alternative criteria for defining depression (quote: "diagnosis of depression according to the criteria proposed by Stewart [Stewart 1965] for medically ill patients, with slight additional inclusion criteria suggested by Kathol and Petty [Kathol 1981] [...]", in association with a cut-off score on standardised rating scales, ZSRDS (Zung Self-Rating Depression Scale) greater than 41; 17-item HRSD (Hamilton Rating Scale for Depression) greater than 16).

With regards to the cancer type and stage, three studies had mixed populations (Costa 1985; Holland 1998; Razavi 1996), but the majority of participants suffered from breast cancer. In Fisch 2003, the population was quite equally distributed between breast, thoracic, genitourinary cancer and other types of cancer. Four studies included only women with breast cancer (Musselman 2006; Navari 2008; Pezzella 2001; Van Heeringen 1996). EUCTR2008-002159-25-FR included only people suffering from head and neck cancer. In two studies the cancer stage was not clearly reported (Fisch 2003; Razavi 1996). Two studies included only people with early stages ("localized" or "early locally advanced" disease) (Navari 2008; Van Heeringen 1996), while all other studies also recruited people with late-stage disease (Costa 1985; EUCTR2008-002159-25-FR; Holland 1998; Musselman 2006; Pezzella 2001).

Outcomes

For efficacy outcomes most of the RCTs provided continuous data such as mean score or mean change on standardised rating scales, including those considered reliable for the aims of this review, such as HRSD (Costa 1985; Musselman 2006; Van Heeringen 1996), MADRS (EUCTR2008-002159-25-FR; Razavi 1996), or other scales (Fisch 2003; Pezzella 2001). One study, Navari 2008, provided only dichotomous data, defining "responders" those who achieved a certain improvement in the rating scale score. Navari 2008 provided these data only for the six-month assessment and thus could not be included in the meta-analysis.

For secondary outcomes, the majority of the studies provided complete data on total dropouts, dropouts due to inefficacy and dropouts due to side effects. Two studies provided only partial data on dropouts (Fisch 2003; Navari 2008). Very few studies reported data on other secondary outcomes, such as social adjustment (Pezzella 2001), and quality of life (Fisch 2003; Pezzella 2001).

A total of 479 people were included in the efficacy analysis on a continuous outcome between six and 12 weeks (primary outcome) and 592 on a dichotomous outcome, 175 in the social adjustments analysis, 305 in the quality of life analysis and 668 in the acceptability analysis.

Excluded studies

We excluded most of the retrieved references after the check of titles and abstracts. Seventy-seven studies needed a full-text examination. Nine studies were included. Among the 68 excluded studies, one was ongoing, 12 were double reports and four were awaiting assessment (Figure 1). We considered 51 studies not eligible, mostly due to a wrong diagnostic status. In particular, one study did not enrol patients with cancer, while in 27 studies patients were not depressed when enrolled and three studies enrolled a population with mixed psychiatric symptoms (e.g. both anxious and depressed patients). Eight studies were not randomised and one was actually a review of other studies. For eight studies the comparison group was not reliable because no placebo or active comparator were employed. For three studies, for which only the abstract or the protocol was available, we contacted the authors who informed us that these studies had been withdrawn or relevantly changed in their design. Details are reported in Characteristics of excluded studies.

Risk of bias in included studies

We found overall the methodological quality of the included studies to be unclear or low (see Figure 2; Figure 3). Only four studies had a low risk of bias for at least one item (EUCTR2008-002159-25-FR; Fisch 2003; Musselman 2006; Pezzella 2001).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

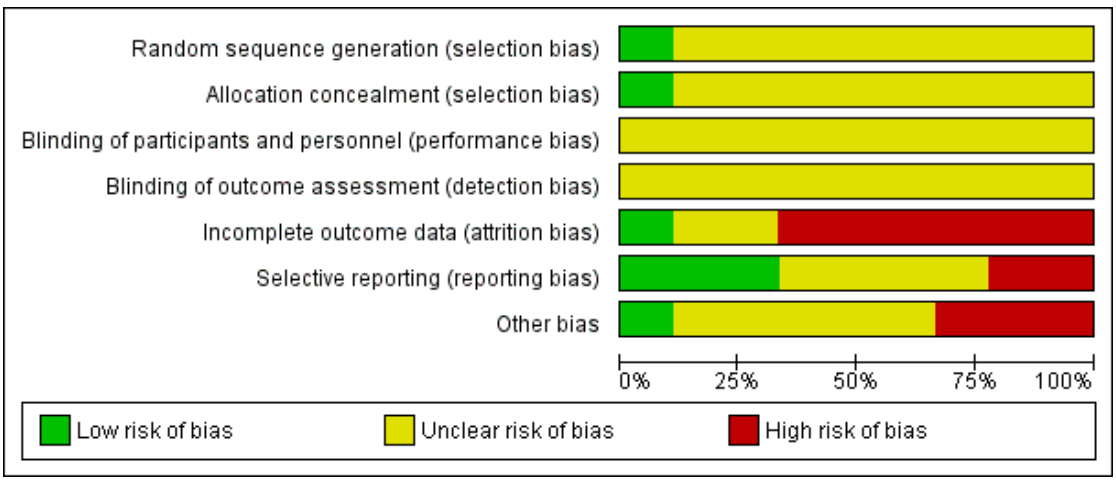
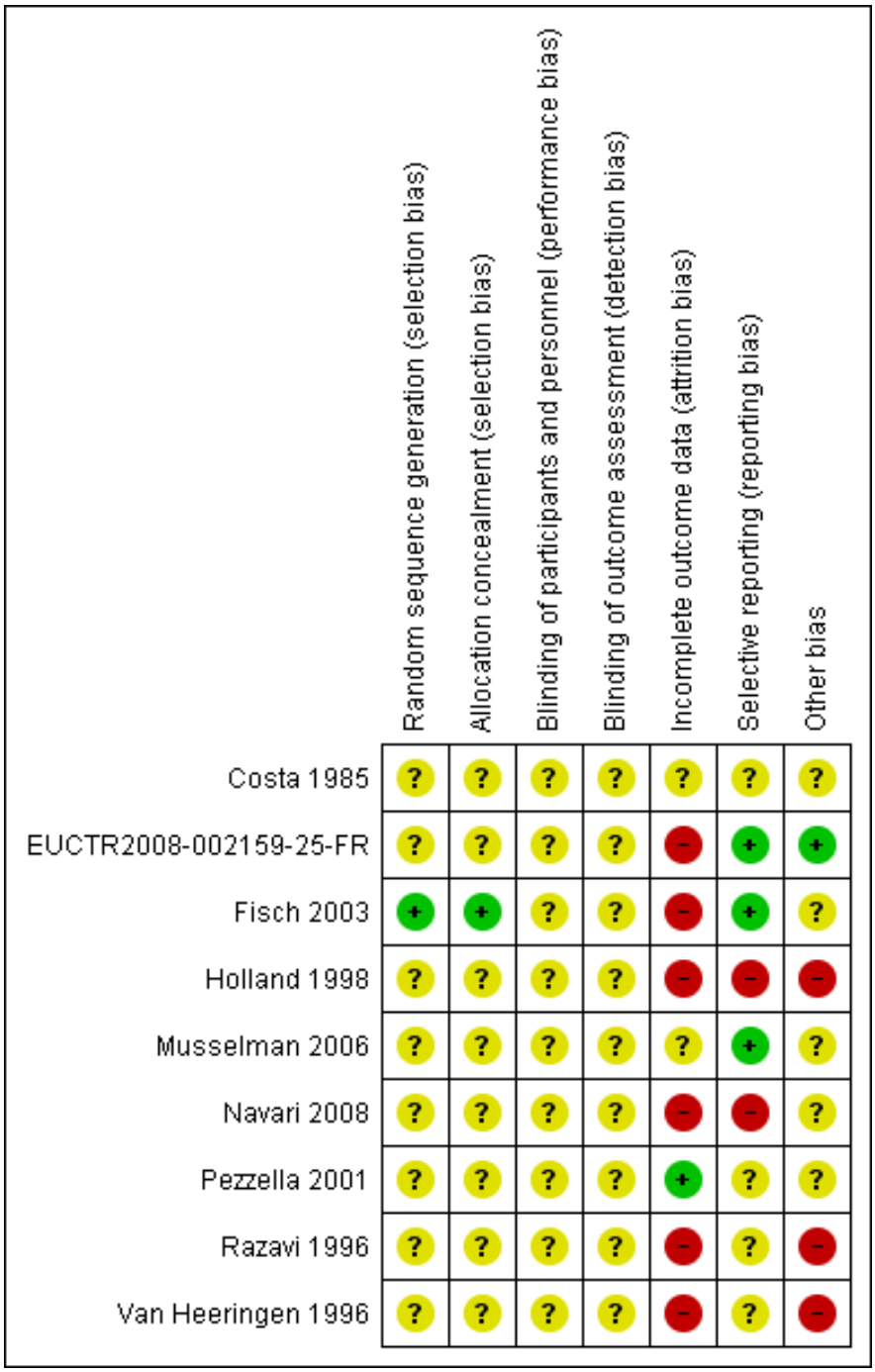


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Almost all the studies had an 'unclear risk' for the selection bias domain, which includes random sequence generation and allocation concealment, because procedures for ensuring adequate concealment allocation were not reported in the paper or in the protocol and because information about the adequacy of the allocation sequence generation were not provided. Only one study, Fisch 2003, clearly described the procedures for randomisation and allocation of participants, which were properly performed.

Blinding

We considered all the included studies to have an 'unclear risk'. They were described as "double-blind", however who was blinded among practitioners, outcome assessors and statisticians was never reported, and procedures for ensuring the blinding of both participants and who administered the intervention were not described.

Incomplete outcome data

The risk of attrition bias appeared to be a particularly relevant issue with different reasons between studies. We considered six studies to have a 'high risk' because no imputation for missing data was performed, resulting in a 'per protocol analysis' or an 'as treated analysis' (even if the term 'intention-to-treat analysis' was often reported) (EUCTR2008-002159-25-FR; Fisch 2003; Holland 1998; Navari 2008; Razavi 1996; Van Heeringen 1996). Furthermore, in three of these studies this issue was associated with a dropout rate higher than 20% at least in one arm, which could possibly induce bias in the intervention effect estimate (Holland 1998; Razavi 1996; Van Heeringen 1996). For two studies we considered the risk 'unclear' as the intention-to-treat analysis was properly performed (Costa 1985; Musselman 2006), but the dropout rate was particularly high (40.5% in the placebo arm in Costa 1985; 38% the paroxetine arm, 36% in the desipramine arm and 45% in the placebo arm in Musselman 2006). For only one study, Pezzella 2001, we considered the risk to be 'low' since the intention-to-treat analysis was properly performed and the dropout rate was not particularly relevant.

Selective reporting

The risk of reporting bias was particularly inconsistent between studies. For two studies the risk was 'high' as primary outcomes were not clearly pre-specified and were poorly reported in the text (Holland 1998; Navari 2008). For four studies the risk was 'unclear' as primary outcomes were not clearly pre-specified, but relevant outcomes of interest were properly reported in the results (Costa 1985; Pezzella 2001; Razavi 1996; Van Heeringen 1996). For the remaining studies all the pre-specified primary outcomes were reported for the time points of interest (EUCTR2008-002159-25-FR; Fisch 2003; Musselman 2006).

Other potential sources of bias

With regards to the possible occurrence of other types of bias, we found no relevant baseline imbalance of the population composition. Furthermore, we systematically assessed the risk of sponsorship bias and in five studies this bias could not be ruled out since the possible conflicts of interest, as well as the role of funders in planning, conducting and writing the study were not discussed (Costa 1985; Fisch 2003; Musselman 2006; Navari 2008; Pezzella 2001). For these studies we considered the risk to be 'unclear'. For three studies we considered the risk to be 'high', as the funder was a pharmaceutical company and its role in planning, conducting and writing the study was not discussed (Holland 1998; Razavi 1996; Van Heeringen 1996). In one study a pharmaceutical company funded the cost of drugs but did not play any relevant role in planning, conducting and writing the study (EUCTR2008-002159-25-FR).

Effects of interventions

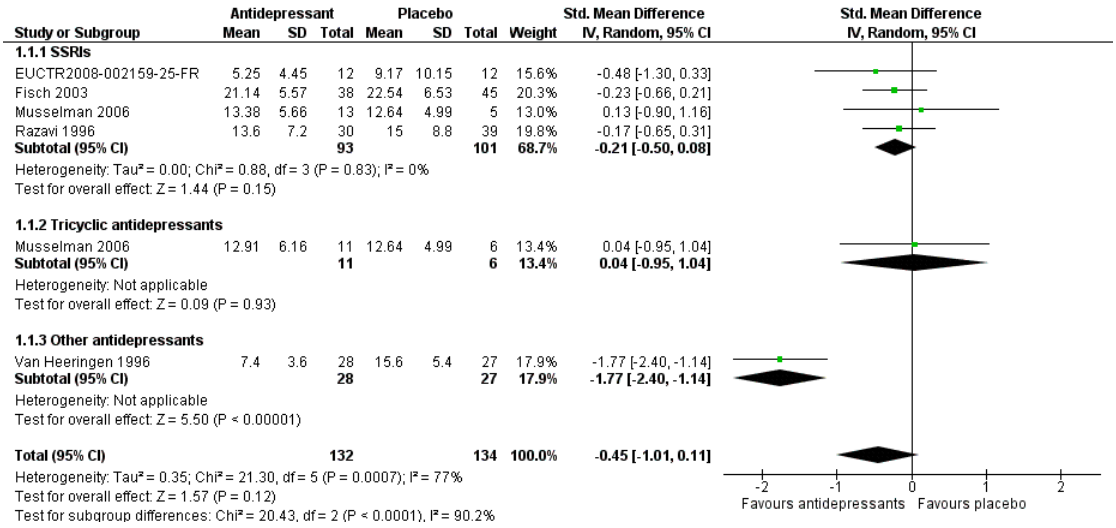
See: **Summary of findings for the main comparison** Antidepressants compared to placebo for patients with cancer and depression; **Summary of findings 2** Selective serotonin reuptake inhibitors (SSRIs) compared to tricyclic antidepressants (TCAs) for patients with cancer and depression

Primary outcome: efficacy at 6 to 12 weeks (continuous outcome)

1.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo, with a standardised mean difference (SMD) of -0.45(95% confidence interval (CI) -1.01 to 0.11, five randomised controlled trials (RCTs), 266 participants) (see Analysis 1.1; Figure 4).

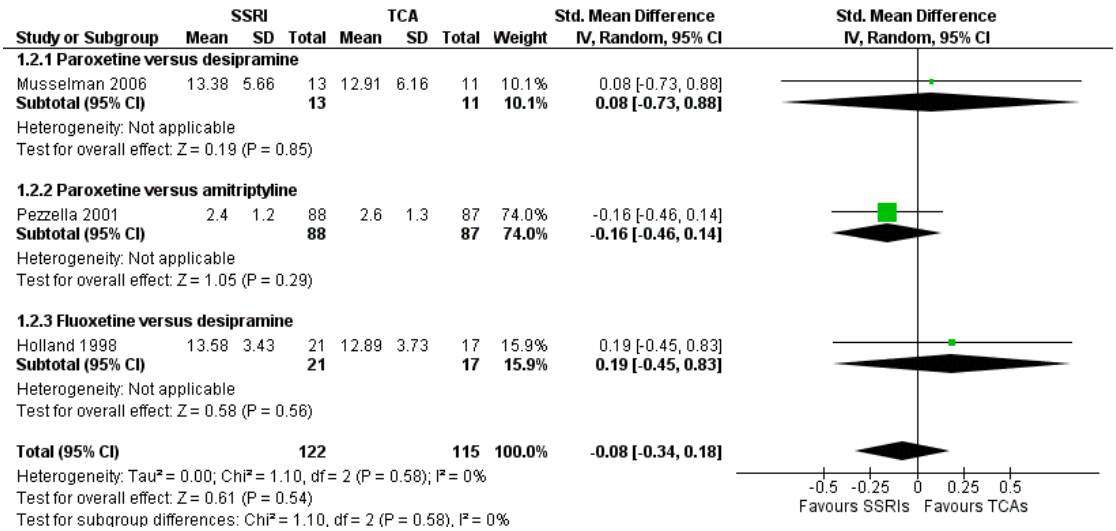
Figure 4. Forest plot of comparison: 1 Depression: efficacy at 6-12 weeks (continuous outcome), outcome: 1.1 Antidepressants versus placebo.



1.2 Antidepressants versus antidepressants

We found no statistically significant difference between selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) as classes, with a SMD of -0.08(95% CI -0.34 to 0.18, three RCTs, 237 participants) (see Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Depression: efficacy at 6-12 weeks (continuous outcome), outcome: 1.2 Antidepressants versus Antidepressants.



Secondary outcomes

2 Efficacy at one to four weeks (continuous outcome)

2.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo, with a SMD of -0.3(95% CI -0.8 to 0.2, four RCTs, 287 participants) (see Analysis 2.1).

- For antidepressants versus antidepressants no studies provided data for this outcome.
- For efficacy after 12 weeks (continuous outcome) no studies provided data for this outcome.

3 Efficacy at 6 to 12 weeks (dichotomous outcome)

3.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo in terms of response rate, with a risk ratio of 0.82(95% CI 0.62 to 1.08, five RCTs, 417 participants) (see Analysis 3.1).

3.2 Antidepressants versus antidepressants

We found no statistically significant difference in terms of response rate between SSRIs and TCAs as classes, with a RR of 1.10(95% CI 0.78 to 1.53, two RCTs, 199 participants) (see Analysis 3.2).

4 Social adjustment at 6 to 12 weeks

4.1 Antidepressants versus antidepressants

Only one study provided data for this outcome, showing no statistically significant difference between paroxetine and amitriptyline, with a mean difference (MD) of 0.10(95% CI -0.38 to 0.58, 175 participants) (see Analysis 4.1).

- For Antidepressants versus placebo no studies provided data for this outcome.

5 Quality of life at 6 to 12 weeks

5.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo, with a SMD of 0.05(95% CI -0.27 to 0.37, two RCTs, 152 participants) (see Analysis 5.1).

5.2 Antidepressants versus antidepressants

Only one study provided data for this outcome, showing no statistically significant difference between paroxetine and amitriptyline, with a SMD of 6.50(95% CI 0.21 to 12.79, 153 participants) (see Analysis 5.2).

6 Acceptability (dropouts due to inefficacy)

6.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo, with a RR of 0.41 (95% CI 0.13 to 1.32, four RCTs, 455 participants) (see Analysis 6.1).

6.2 Antidepressants versus antidepressants

We found no statistically significant difference between SSRIs and TCAs as classes, with a RR of 0.85(95% CI 0.14 to 5.06, three RCTs, 237 participants) (see Analysis 6.2).

7 Acceptability (dropouts due to side effects)

7.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo, with a RR of 1.19(95% CI 0.52 to 2.72, six RCTs, 455 participants) (see Analysis 7.1).

7.2 Antidepressants versus antidepressants

We found no statistically significant difference between SSRIs and TCAs as classes, with a RR of 1.04(95% CI 0.55 to 1.99, three RCTs, 237 participants) (see Analysis 7.2).

8 Acceptability (dropouts due to any cause)

8.1 Antidepressants versus placebo

We found no statistically significant difference between antidepressants as a class and placebo, with a RR of 0.87(95% CI 0.49 to 1.53, six RCTs, 455 participants) (see Analysis 8.1).

8.2 Antidepressants versus antidepressants

We found no statistically significant difference between SSRIs and TCAs as classes, with a RR of 0.83(95% CI 0.53 to 1.30, three RCTs, 237 participants) (see Analysis 8.2).

Subgroup analyses

1. Psychiatric diagnosis

Results from this subgroup analysis did not materially change the main findings for the primary outcome, which remains not statistically significant in both people with major depressive disorder and people with adjustment disorder, dysthymic disorder or depressive symptoms. This is true for both the 'antidepressant-placebo' and the 'head-to-head' comparison (see Analysis 9.1 and Analysis 9.2).

2. Previous history of depressive conditions

We did not perform this analysis since the data provided were not sufficient to measure the primary outcome in this subgroup of participants.

3. Antidepressant class

In the main analysis we pooled data separating the following classes of antidepressants: SSRIs, TCAs and other antidepressants. Considering the 'antidepressant-placebo' comparison, we found no statistically significant effect for both SSRIs (SMD -0.21, 95% CI -0.50 to 0.08, four RCTs, 194 participants) and TCAs (MD 0.27, 95% CI -5.13 to 5.67, one trial, 17 participants). However, we found mianserin, the only compound in the 'other antidepressants' class, to be effective over placebo (MD -8.2, 95% CI -10.6 to -5.77, one trial, 55 participants) (see Analysis 1.1). In this analysis MDs are reported as SMDs. The difference between the subgroups was statistically significant (P value < 0.0001). The 'head-to-head' comparison did not show statistically significant differences between SSRIs and TCAs as classes (SMD -0.08, 95% CI -0.34 to 0.18, three studies, 237 participants) (see Analysis 1.2).

4. Cancer site

Results from this subgroup analysis did not materially change the main findings for the primary outcome. No statistically significant effect was found when pooling studies that enrolled only women with breast cancer (see Analysis 10.1 and Analysis 10.2). It was technically feasible to separate these two subgroups, however the 'other sites' subgroup could not be considered a reliable comparison with the 'breast cancer' subgroup because, even if in these studies people with different types of cancer were enrolled, the vast majority of them were actually affected by breast cancer.

5. Cancer stage

Results from this subgroup analysis did not materially change the main findings for the primary outcome (see Analysis 11.1 and Analysis 11.2). Two studies among those comparing antidepressants versus placebo enrolled only people with late stage disease (Costa 1985; Holland 1998), however the study Costa 1985 did not provide data for the primary outcome (efficacy at 6 to 12 weeks) and was not included in the analysis. Other studies had a mixed population in terms of cancer stage, with the exception of Razavi 1996, in which only people in a stage 0 (carcinoma in situ, early form) were enrolled. Considering the 'head-to-head' comparison, only one study, Holland 1998, enrolled people with early stage disease, showing no statistically significant differences between SSRIs and TCAs as classes (MD 0.69, 95% CI -1.61 to 2.99, one trial, 38 participants), while other studies had a mixed population.

6. Gender

This analysis is encompassed in the 'cancer site' analysis, because the 'female participant' subgroup matches with the 'breast cancer' subgroup (see Analysis 10.1). A subgroup analysis for male only was not feasible, since other studies enrolled both male and female participants.

Sensitivity analyses

1. Excluding trials in which the randomisation process is not clearly reported

We did not perform this sensitivity analysis because no studies, with the exception of Fisch 2003, reported clear details on random sequence generation and concealment of random allocation.

2. Excluding trials with unclear concealment of random allocation

See above.

3. Excluding trials that did not employ adequate blinding of participants, healthcare providers and outcome assessors

We did not perform this sensitivity analysis because no studies reported clear details on the procedures for ensuring blindness.

4. Excluding trials that did not employ depressive symptoms as their primary outcome

Only one study assessed depressive symptoms as a secondary outcome (Fisch 2003), and it contributed only to the 'antidepressants versus placebo' analysis. Results from this sensitivity analysis did not materially change the main findings for the primary outcome (see Analysis 12.1).

5. Excluding trials with imputed data

Five studies did not impute missing data, applying a 'per protocol' or an 'as treated' analysis (EUCTR2008-002159-25-FR; Fisch 2003; Navari 2008; Razavi 1996; Van Heeringen 1996). These

studies contributed only to the 'antidepressants versus placebo' analysis. After removing trials with imputed data the meta-analysis still did not show a statistically significant superiority of antidepressants over placebo, with a SMD of -0.64(95% CI -1.35 to 0.06, four trials, 231 participants) (see Analysis 13.1).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

SSRIs compared to TCAs for patients with cancer and depression

Patient or population: patients with cancer and depression
Settings: in- and outpatients
Intervention: SSRIs
Comparison: TCAs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	TCAs	SSRIs				
Efficacy as a continuous outcome Follow-up: 6 to 12 weeks		The mean efficacy as a continuous outcome (SMD) in the intervention groups was **0.08 standard deviations lower** (0.34 lower to 0.18 higher)		237 (3 studies)	⊕◯◯◯ **very low**[1,2,3]	
Efficacy as a dichotomous outcome Follow-up: 6 to 12 weeks	**Study population**		**RR 1.17** (0.66 to 2.06)	199 (2 studies)	⊕◯◯◯ **very low**[1,2]	
	388 per 1000	**454 per 1000** (256 to 799)				

Acceptability - drop-outs due to any cause Follow-up: 4 to 12 weeks	**Study population**		**RR 0.83** (0.53 to 1.3)	237 (3 studies)	⊕◯◯◯ **very low**[1,2,3]
	261 per 1000	**217 per 1000** (138 to 339)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **SMD:** standardised mean difference; **SSRI:** selective serotonin reuptake inhibitor; **TCA:** tricyclic antidepressant

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No studies described the outcome assessment as masked. This should be considered a major limitation, which is likely to result in a biased assessment of the intervention effect.
[2]Very low number of participants recruited (fewer than 100 individuals in both treatment arms) and 95% CI includes both no effect and appreciable benefit or appreciable harm, which suggests the risk of very serious imprecision of the results and thus low confidence in their reliability.
[3]One study out of three had a high risk of sponsorship bias.

DISCUSSION

Summary of main results

The present systematic review included a total of nine randomised controlled trials (RCTs), involving 861 participants. The included studies did not report all the outcomes that were pre-specified in the protocol. Seven of the RCTs provided continuous data, which contributed to the meta-analysis for the primary outcome (Analysis 1.1; Analysis 1.2). Only one study, Navari 2008, did not provide data suitable for the meta-analysis. The majority of studies provided detailed data on dropouts, while for some other secondary outcomes very few trials (Analysis 4.1; Analysis 5.1; Analysis 5.2) or no trials (Analysis 4.1) provided data.

Overall, we detected no evidence of a difference between antidepressants as a class and placebo in terms of efficacy (both on continuous and dichotomous outcomes) and acceptability. For the primary outcome ('efficacy as a continuous outcome at 6 to 12 weeks') we found only mianserin to be effective over placebo. For the primary outcome, the sensitivity analysis excluding trials with imputed data gave similar results. We cannot rule out benefit in the early response phase (one to four weeks), but this comes from an analysis with substantial statistical variation. No trials assessed follow-up response (more than 12 weeks). In head-to-head comparisons, we retrieved only data for selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs) and found no difference between these two classes.

For the secondary outcome 'remission rate at 6 to 12 weeks', we found no differences for both the antidepressant-placebo and the head-to-head comparison. Very few studies contributed to the secondary outcomes 'social adjustment' and 'quality of life', and thus no relevant findings emerged. For the secondary outcome acceptability, we found only mianserin to have a statistically significant lower dropout due to inefficacy and dropout due to any cause compared with placebo. In head-to-head comparisons we retrieved only data for SSRIs versus TCAs and found no difference between these two classes.

Overall completeness and applicability of evidence

The study population was quite homogeneous in terms of cancer diagnosis. The vast majority of people were affected by breast cancer. Some degree of heterogeneity was found in terms of stage of cancer, anti-cancer treatments and psychiatric diagnosis, including different depressive conditions. Beside that, the overall number of participants was very low, and thus this population could hardly reflect the complexity of people with cancer from a 'real world' setting. Furthermore, it is worth noting that no studies were conducted in elderly patients only, although this population represents a relevant part of the oncologic population.

The majority of studies enrolled a very small number of participants and did not provide data for all the outcomes specified in the protocol. For these reasons most of the analyses were underpowered and this relevantly limits the overall completeness of evidence. In particular, we chose to consider efficacy as a continuous outcome at 6 to 12 weeks as the primary outcome, being in our opinion a more reliable outcome for these people in clinical practice. However, some trials were excluded from this analysis, for not reporting continuous outcomes or performing the assessment at a different time point.

Another compelling issue was retrieving data from unpublished studies. Even after having found a relatively consistent number of unpublished trials in the above mentioned online registers, reliable data to be included in the meta-analysis were not available. Very few authors replied to our request for information or data and only one unpublished study was included. One trial was clearly ongoing and we classified four studies as 'awaiting classification', being eligible according to the protocol or the abstract, but not providing any data feasible for the meta-analysis. Considering the overall small number of studies included and the uncertainty of the meta-analysis results, it is plausible that these studies could have made a relevant difference in our analysis.

We chose to consider only the dropout rate due to adverse events as a proxy of the acceptability of treatments because in this particular population the most common side effects of antidepressants (e.g. asthenia, sedation, headache, nausea and gastrointestinal problems) are very likely to be caused also by other anti-cancer therapies, pain syndromes or the direct effects of cancer. We know from previous literature that antidepressants are generally well tolerated by people with medical illness (Rayner 2010), even when very complex and advanced (including people with cancer) (Rayner 2011a). However, some authors showed possible toxicities of antidepressants in this population (Stockler 2007). For this reason, further analysis may be relevant for assessing the occurrence of adverse effects likely linked to the assumption of antidepressants.

It has been suggested that the efficacy of tamoxifen, a drug broadly used for prevention and treatment of breast cancer, could be lessened by some antidepressants that act on CYP2D6 inhibitors. This would therefore worsen the prognosis of these people in a five-year period (Kelly 2010). The most relevant effect as been shown for paroxetine, however other drugs, such as fluoxetine, bupropion and duloxetine, could theoretically have a similar effect, and should be therefore avoided in these patients (Andrade 2012). This possible effect is unlikely to have affected our analysis, since two studies used paroxetine (Musselman 2006; Pezzella 2001), and only one, Musselman 2006, included participants possibly taking tamoxifen, and the follow-up period was relatively short to appreciate this potentially harmful effect.

Quality of the evidence

The overall methodological quality of the included studies was poor (see Figure 2; Figure 3). No study showed an overall low risk of bias. The majority of studies showed mixed features, with the large prevalence of an 'unclear risk' of bias in different domains (see Figure 3), which seems to reflect the lack of exhaustive reporting rather than a clear evidence of bias. This is consistent with the finding of a general sub-optimal reporting of RCTs in medical journals despite the large diffusion of instruments designed to help transparent reporting, such as the CONSORT Statement (Turner 2012).

The GRADE methodology is a tool to provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison and the magnitude of effect of the interventions examined. The overall confidence in the estimate of effect appeared to be 'very low' for all of the main outcomes assessed (see Summary of findings for the main comparison; Summary of findings 2). This judgement reflects some issues of the included studies, namely the high 'risk of bias' (due to poor methodological quality and high dropout rates), 'inconsistency' (due to the high degree of heterogeneity between studies) and 'imprecision' (due to the low number of participants in each trial and wide confidence intervals). In accordance with that, any estimate of effect should be considered very uncertain, and further research is very likely to change the estimate of effect and thus the degree of confidence for its applicability in routine clinical practice.

Potential biases in the review process

Several possible limitations of this review should be highlighted, and thus the interpretation of results should remain provisional and tentative.

Some limitations are intrinsically related to the actual process of retrieving, collecting, selecting and extracting data. In order to reduce the potential bias of this complex process two authors independently worked on each of these steps. With regards to the selection of relevant studies, the degree of agreement between the two authors was evaluated with the calculation of 'simple kappa statistics', which confirmed the reliability of the selection process (see Results of the search). It has been highlighted that two independent extractors are overall more reliable than the extraction performed by a single author followed by verification by a second author (Buscemi 2006). We applied the same process for the 'Risk of bias' assessment. Furthermore, disagreements were discussed with a third author, who also checked the data extracted from RCTs when the analysis was performed. Another relevant problem concerns the 'systematic' nature of the search. We chose to include only randomised trials as they provide the strongest level of evidence available. In this type of review there is some risk of publication bias, which means that negative studies may have not been published. Some authors of this review are expert in the field, thus it is unlikely that significant studies were overlooked. However, although the search was thorough, it is possible that there are still unpublished studies which have not been identified, considering that there are no shared procedures to perform this kind of search (Chan 2012). The impact of unpublished literature on the results of this review is uncertain, however it is expected that the analysis of only published literature would lead to overestimation of the efficacy of a given intervention (Turner 2008). Moreover, the search date is April 2014 and there are four studies classified as 'awaiting assessment', the eligibility of which has yet to be determined. At the end of this process, we identified very few studies and the data of interest obtained were relatively limited.

It is important to bear in mind that some of the included studies were funded by the pharmaceutical industry, and this may again introduce an overestimation of the efficacy of interventions.

To assess efficacy, we gave preference to rating scales administered by clinicians or expert assessors (Hamilton Rating Scale for Depression - HRSD, Montgomery and Åsberg Depression Rating Scale - MADRS, Clinical Global Impression Rating scale - CGI). Even though they are standardised tools commonly used in antidepressant trials, they are all potentially prone to observer bias. For three studies self administered questionnaires were used (EUCTR2008-002159-25-FR; Fisch 2003; Navari 2008). We noted some heterogeneity in terms of outcome measurement, and this might represent a limitation in interpreting the effect of interventions. For instance, in Analysis 1.1, Analysis 2.1, Analysis 6.1 and Analysis 8.1 only the study Van Heeringen 1996 shows a clear beneficial effect of the antidepressant (in this case, mianserin) over placebo, which deeply affects the final result of the meta-analyses. In general, the positive effect shown in the mianserin studies (Costa 1985; Van Heeringen 1996) had a relevant impact on overall results (see Analysis 2.1; Analysis 3.1). Another limitation is the use of non-specific rating scales, designed for assessing specific psychiatric symptoms and domains, rather than mood disorders in medically ill people.

One important limitation of the included trials (and consequently of the present review) is that not all studies reported a continuous outcome for the chosen time points, underpowering the analyses and undermining the possibility of finding significant differences between comparisons.

Quality of life (QoL) and social functioning were rarely reported in the included studies. This possibly limits our interpretation of the efficacy of intervention, which should not be focused only on depression, considering that comorbid depressive symptoms deeply impact the overall burden of disease alongside QoL and functioning (Arrieta 2013). Some authors also described a relevant impact of comorbid depression on cancer mortality (Lloyd-Williams 2009; Pinquart 2010; Satin 2009). This outcome was not described in the included studies, due to relatively short periods of follow-up.

The dropout rate due to any cause is considered the most consistent measure for the outcome 'acceptability', which encompasses not only dropouts due to adverse events, but also due to efficacy and any other cause. However, this is only a proxy measure for this

outcome, since it comprises very heterogeneous reasons for leaving the study early, detailed description of which was beyond the aim of this review.

For one three-arm study, Musselman 2006, which compared paroxetine versus desipramine versus placebo, we chose to split the 'shared' group (in this case the placebo group) into two groups with smaller sample size, in order not to report in the analysis the same subpopulation of patients. These smaller groups contributed to one comparison each (namely paroxetine versus placebo and desipramine versus placebo). In the analysis of dichotomous outcomes the number of events was also split between the two comparisons. This method, although considered reliable according to the *Cochrane Handbook for Systematic Reviews of Interventions* (16.5.4) (Higgins 2011), is not the most recommended since it only partially overcomes the unit of analysis error (because the resulting comparisons remain correlated). In this case, however, this approach allowed us to perform a detailed subgroup analysis for antidepressant classes. Alternatively, the two antidepressant arms should have been pooled together and compared with the placebo group. However, these two drugs has different mechanisms of action and thus are not expected to share a 'class effect', and this would have created an artificial arm, which does not exist in clinical practice.

Finally, it is very relevant to note that people suffering from different types and stages of cancer can hardly be considered as a homogeneous group, considering that there are several differences in genetic, biological and immunological mechanisms, as well as in physical and psychosocial impairment. Due to the paucity of data, several subgroup analyses that should have investigated these characteristics were not feasible. Moreover, we were able to perform only a few subgroup analyses, which were in turn underpinned by poor data. We cautiously interpreted the results from these analyses, since multiple calculations may risk producing a result that is statistically significant by chance alone.

Agreements and disagreements with other studies or reviews

Analyses from this study draw a different picture with respect to previous reviews and meta-analyses. Results from the meta-analyses by Hart 2012 and Walker 2014 are hardly comparable to the present study, since they enrolled only patients with "elevated depressive symptoms" and a formal diagnosis of major depression, respectively. Conversely, the meta-analysis by Laoutidis 2013 included the same studies as our review, with the only difference of one unpublished study (EUCTR2008-002159-25-FR). In Laoutidis 2013, a superiority of antidepressants versus placebo in terms of 'therapeutic response' (as a dichotomous outcome) was shown, with a risk ratio of 1.56 (95% confidence interval (CI) 1.07 to 2.28, P value = 0.021). This analysis slightly differs from the one performed in the present study, where no statistically significant difference was found (see Analysis 3.1). In contrast with the meta-analysis by Laoutidis 2013, the study carried out by Navari and colleagues (Navari 2008) was not eligible for this analysis as our focus was the 'acute phase treatment response' (between 6 and 12 weeks), while this study reported the number of responders at week 24. Other differences refer to different approaches employed in the definition of some intention-to-treat (ITT) populations. Moreover, in Laoutidis 2013 no analyses of continuous outcomes were performed and similarly to our analysis no differences between SSRIs and TCAs were found. Additionally, the review and meta-analysis by Riblet 2014 is difficult to compare with the present one, as it included some trials that were excluded from our analysis, in particular one quasi-randomised trial (Wang 2011), and two trials where patients were not depressed at baseline (Del Carmen 1990; Roscoe 2005).

The use of antidepressants in people with cancer has been studied in many different ways in the scientific literature, focusing not only on treating depressive symptoms or disorders, but also on preventing depression (e.g. in one study, Morrow 2003, antidepressants appeared effective in a population of 549 patients), or treating some cancer-related symptoms, such as hot flushes, fatigue, insomnia, hyporexia and weigh loss, etc. For the majority of these studies people were enrolled on the basis of medical symptoms and a proper assessment of concomitant depressive conditions was not always performed. These RCTs provided contrasting findings, showing both positive (Roscoe 2005) and null effect (Kimmick 2006; Musselman 2013; Stockler 2007) of antidepressants over placebo. These studies, however, may broaden the discussion about the clinical suitability of antidepressants in people with cancer, since it has been claimed that a continuum of depressive experiences, ranging from distressing cancer-related symptoms to proper depressive symptoms or disorders, can be detected in this population (Brenne 2013; Mitchell 2011; Raison 2003).

Some non-randomised studies were retrieved (Biglia 2005; Caldera 2009; Evans 1988; KCT0000076; NCT00234195; NCT01725048; Tondlova 1997), however for most of them only conference procedures or protocols were available. Moreover, results from the remaining studies can hardly provide a relevant contribution to the discussion, since they were performed on very small populations of patients (Biglia 2005; Evans 1988).

We retrieved one ongoing study (NCT01598584), and classified three studies as 'awaiting assessment' (N0405078066; NCT00066859; NCT00387348). Data from these studies, even partial or provisional, were not available, thus their possible impact remains unclear.

Given the relevant amount of literature on this topic, the role of antidepressant drugs in this group of people seems to represent a relevant issue in routine clinical practice. However, clear indications from this heterogeneous literature cannot be easily derived.

AUTHORS' CONCLUSIONS

Implications for practice

There is a very low number of randomised trials assessing the efficacy of antidepressants in cancer patients, despite the relevance of this issue. Moreover, evidence for the effects we have found in terms of the efficacy and acceptability of antidepressants in people with cancer is of very low quality. Data from the present review failed to reveal any statistically significant beneficial effect of these drugs over placebo, with the only exception of mianserin (see Figure 4). Although this drug was compared with placebo in two studies only, with small number of included participants, it showed some beneficial effects in terms of efficacy and acceptability. Mianserin is often used in oncological settings for its beneficial profile on sleep and appetite, as well as mood. Conversely, this drug is seldom used in routine clinical practice in psychiatric settings and very few data from randomised controlled trials (RCTs) are available on its efficacy in people with major depression. This compound is considered to have a similar profile to mirtazapine, the efficacy of which has been largely shown, but with a possible unfavourable tolerability profile with respect to selective serotonin reuptake inhibitors (SSRIs) (Cipriani 2009). The efficacy and acceptability of these drugs in severe medically ill people is yet to be assessed. Thus, the clinical meaning of these results is uncertain and no clear implications for clinical practice can be drawn. Similarly, no significant differences between one drug and another emerged (see Figure 5).

An appropriate treatment for depressive symptoms in people with cancer is a relevant goal in routine clinical practice, as shown by the ongoing discussion in the scientific literature. There is a growing awareness of the need for a multi-dimensional approach, encompassing biological, social and psychological issues, as highlighted by previous reviews (Akechi 2008; Galway 2012). A proper evaluation of subthreshold depressive symptoms seems essential, also considering their potentially relevant impact on the prognosis of cancer, although it is not easy to discern when it is worthwhile to introduce an antidepressant. Very few and unspecific indications could be derived from the available guidelines (NICE 2009; Rayner 2011b). In general, based on the results of the current review, the possible role of antidepressants is still controversial and should be assessed each time by the clinician on an individual basis. The choice of which antidepressant should be prescribed can hardly be made on the basis of this review, and rather it may be based on the data on antidepressant efficacy in the general population of individuals with major depression. Additionally, the data on antidepressant efficacy in medically ill people, which suggest a positive safety profile of SSRIs (Rayner 2010; Rayner 2011a), may also be considered.

Implications for research

The results described in this systematic review come from evidence of very low quality according to the GRADE methodology. Moreover, in many cases studies were financially supported by pharmaceutical industries. Consequently, there is a high risk that these studies do not provide sufficient and adequate information for clinicians in real-world settings. The present review highlights the strong need for further studies, which should be conducted to high methodological standards and with the primary intent of providing clinicians with useful practical data on the effectiveness of antidepressant drugs, firstly over placebo and subsequently in head-to-head comparisons. Alongside rating scales, pragmatic outcome measures, such as quality of life and social functioning, should also be considered.

Despite the high prevalence of depression in people with cancer and its massive impact, the number of randomised trials assessing the efficacy of antidepressants in oncology is still very low. We recognise that these studies are extremely difficult to conduct, as depression is not always considered a major concern by doctors and by people with cancer, who are sometimes reluctant to admit its existence. Moreover, promoting this type of trials may be not considered as a priority for anti-cancer research funding agencies.

Further basic research on the pathogenetic pathways of depression in medically ill people is needed. This could be helpful for identifying possible therapeutic targets, and would also allow the assessment of new, possibly effective drugs with comparative study designs.

Generally SSRIs are considered to have a good therapeutic index among antidepressants. However, some other antidepressants could be theoretically helpful in this particular population, being possibly effective not only for depression, but also for medical symptoms. For example, some non-controlled studies are available on the effect of mirtazapine for insomnia and hyporexia, or duloxetine for pain perception, hot flushes and so on. In actuality no randomised trials in people with cancer are available with these compounds.

In order to increase the evidence base on this compelling issue we argue that large, simple, randomised, pragmatic RCTs comparing commonly used antidepressants (SSRIs, serotonin-norepinephrine reuptake inhibitor (SNRIs), mirtazapine) versus placebo should be conducted in individuals with cancer and depressive symptoms, with or without a formal diagnosis of a depressive disorder.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Costa 1985

Methods	8-week, randomised study
Participants	Female participants, age 18 years and over, affected by cancer (mixed sites, including breast, ovary, uterine cervix and others) at any stage, diagnosed with depression, according to the criteria proposed by Stewart 1965 for medically ill patients, with slight additional inclusion criteria suggested by Kathol and Petty (7): (i) low mood and loss of interest for at least 3 weeks; (ii) at least 4 of the following: difficulty in concentration or memory problems, irritability, feelings of worthlessness or hopelessness, fear of losing one's mind, lack of initiative, frequent crying or wanting to die, suicide attempt; (iii) social impairment at work, home etc; (iv) anorexia, sleep disturbance, fatigue, motor retardation. Further inclusion criteria were depression succeeding or paralleling development of cancer; Zung Self-Rating Depression Scale (ZSRDS) score greater than 41; Hamilton Depression Rating Scale (HDRS) items 1 to 17 score greater than 16; and informed consent of the patient. Participants were mostly inpatients, but rates of in- and outpatients are not reported
Interventions	Mianserin: 36 participants. The dose was flexible starting from 10 mg 1 tablet per day in the first week and 2 tablets per day from the second week (range not reported; mean dose between weeks 1 and 4 was 44.5 mg/day) Placebo: 37 participants
Outcomes	Efficacy and tolerability of mianserin versus placebo, assessed with Zung Self-Rating Depression Scale (ZSRDS); Hamilton Depression Rating Scale (HDRS-17); Clinical Global Impression Scale for Severity of Illness (CGI-S); Clinical Global Impression Scale for Severity of Illness (CGI-I), Efficacy Index (EI) and a checklist for somatic findings and side effects
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"; no further details on the sequence generation process. However, quote: "Treatment groups were well matched for social data (education, occupation and marital status) [not reported in tables]. Treatment groups were also well matched for main cancer localizations, clinical stages of cancer, and baseline Karnofsky scores [reported in tables]."
Allocation concealment (selection bias)	Unclear risk	Not reported

Costa 1985 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patient compliance and physician blindness were good throughout the trial. Thus, the number of psychiatrist's correct guesses as to which treatment the patients were receiving (22, mianserin; 16, placebo) were not significantly higher than expected by chance". Procedures for ensuring the blinding of both participants and who administered the intervention are not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Efficacy was evaluated using double-blind assessment...". No further clarifications on which procedure was used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates: in the mianserin group 7/36 (19.4%), in the placebo group 15/37 (40.5%). The imbalance in total rates and possible different reason for losses between groups is not discussed. All randomised participants were included in the analysis, which is consistent with an 'intention-to-treat' analysis (but this term is not reported). Quote: "[...] the only treatment comparison known to be unbiased is that based on the analysis of all randomised patients". Missing data were imputed according to the LOCF, quote: "Data used in the statistical analysis of efficacy were based on the 'last assessment carried forward approach' in which missing scores for those patients who dropped out before day 21 had their last observed score assigned to the missing assessment". Even if there was a high dropout rate in the placebo group, the risk of bias was rated as 'unclear' rather than 'high', since the ITT analysis and LOCF imputation were properly performed
Selective reporting (reporting bias)	Unclear risk	Outcomes are not clearly pre-specified in the methods (quote: "[...] compare the efficacy and safety of mianserin in women with cancer [...]"). However, outcomes of interest are properly reported in the results. Scores for HDRS, ZSRDS, CGI-S, EI and the number of participants with each side effect on the checklist were reported for every week. The number of responders is reported, but only according to the CGI-I endpoint scores
Other bias	Unclear risk	Sponsorship bias cannot be ruled out since a 'financial disclosure' or possible conflicts of interest are not reported

EUCTR2008-002159-25-FR

Methods	12 weeks, randomised, double-blind, placebo-controlled study
Participants	People with (a) cancer of the upper aerodigestive tract (buccal cavity, larynx, oropharynx, hypopharynx), solitary or multiple synchronous localisations, stage I to IVb, to be treated by surgery and/or radiotherapy and/or chemotherapy (first-line curative treatment); (b) HADS more than 11 (excluded those with a diagnosis of major depressive episode with severity criteria and/or suicidal thoughts); (c) aged between 18 and 75 years, having signed an informed consent
Interventions	Escitalopram: 20 participants Placebo: 18 participants
Outcomes	Primary outcome: sub-score depression of the HADS, W12 Secondary outcomes: CES-D; MADRS; CGI; SCL-90-R; health-related quality of life (EORTC QLQC-30, H-N 35), alcohol or tobacco consumption (CO, CDT)
Notes	Data were partially provided by the authors before the publication of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported (unpublished study)
Allocation concealment (selection bias)	Unclear risk	Not reported (unpublished study)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported (unpublished study)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported (unpublished study)
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rate: escitalopram arm 4/20 (20%); placebo arm 3/18 (16.7%). Only participants who completed the assessment at each time point were analysed and missing data were not imputed ('per protocol' analysis)
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes are reported for the endpoint assessment (week 12) and for week 4
Other bias	Low risk	The baseline features of the population of the study are not reported. The Gustave Roussy, which is a private non-profit hospi-

EUCTR2008-002159-25-FR (*Continued*)

		tal, was the sponsor of the trial. Lundbeck funded only the costs of drugs and did not play any role in planning, conducting and writing the study

Fisch 2003

Methods	Randomised, placebo-controlled, multicentre (15 centres) study
Participants	Ambulatory people of either sexes with advanced cancer (mixed sites) and depressive symptoms, as assessed with a score of 2 or greater on the Two-Question Screening Survey (TQSS), excluding people with major depression diagnosed by a psychiatrist in the past 6 months. All participants gave informed consent
Interventions	Fluoxetine: 83 participants. The dose was 20 mg/day, fixed Placebo: 80 participants
Outcomes	The primary outcome was the quality of life (QoL) assessed with the Functional Assessment of Cancer Therapy-General (FACT-G, version 3). The secondary outcome was the depressive symptoms assessed with the 11-item BZSDS
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "[...] randomly assigned in a double-blind manner to receive either fluoxetine (20-mg tablets) or an identical placebo tablet. The randomization was performed centrally through a preprinted randomisation table, and the study drug was sent by overnight mail directly to the patient" and "Patients in each study arm were comparable at baseline with respect to age, sex, performance status, symptom status regarding pain and depression, disease distribution, and current treatment with chemotherapy. "
Allocation concealment (selection bias)	Low risk	Quote: "[...] The randomisation was performed centrally through a preprinted randomisation table, and the study drug was sent by overnight mail directly to the patient."

Fisch 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Patients were then randomly assigned in a double-blind manner to receive either fluoxetine (20-mg tablets) or an identical placebo tablet". This should ensure patient blinding. The study is described as 'double-blind', however procedures for ensuring the blinding of who administered the intervention are not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants who completed the assessment at each time point were analysed and missing data were not imputed ('per protocol' analysis). At the 'primary endpoint' (second visit, mean of 4.6 (fluoxetine group) versus 4.7 (placebo group) weeks from baseline) 64 versus 65 participants were assessed (over 83 versus 80 participants randomised). Only dropout rates due to side effects at the end of the study are reported, and whether there was imbalance between groups in term of reasons for leaving the study early is not discussed
Selective reporting (reporting bias)	Low risk	Relevant data for the pre-specified (methods) outcomes are reported (results)
Other bias	Unclear risk	Sponsorship bias cannot be ruled out since a 'financial disclosure' or possible conflicts of interest are not reported

Holland 1998

Methods	6-week, prospective, randomised, double-blind, multicentre (6 investigative sites) study
Participants	Women affected by cancer (mostly breast cancer at stage II, II, IV) and major depressive disorder (for at least 30 days before entering the study) or adjustment disorder with depressed mood (for at least 60 days before entering the study), according to the criteria of DSM-III-R and a score of more than 14 on the first 17 items of the HAM-D. Participants gave signed informed consent
Interventions	Fluoxetine: 17 participants. The dose was 20 mg/day for the first month, thereafter the dose was flexible. However, the maximum dose allowed is not reported Desipramine: 21 participants, starting with a dose of 25 mg/day and titrated in 25 mg/week increments to a dose of 100 mg/day at week 4. Thereafter the dose was flexible to

Holland 1998 (*Continued*)

	a maximum of 150 mg/day There was not a placebo arm, but all participants received placebo+active drug (alternated during the day) in order to maintain the blindness ('double-dummy' approach)
Outcomes	Safety and efficacy of fluoxetine versus desipramine. Depression and anxiety were assessed with the 17-item Hamilton Rating Scale for Depression (HAM-D-17), the Hamilton Anxiety Rating Scale (HAM-A), the Clinical and Patient's Global Impression (CGI and PGI) scales. Quality of life was assessed with the Functional Living Index for Cancer (FLIC), the Memorical Pain Assessment Card (MPAC), and the SF-36 Health Survey. Adverse events were self reported and evaluated weekly through clinical assessment
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "[...] a 6-week, double-blind (randomisation of placebo non-responders) phase [...]. Treatment groups [...] had comparable demographics and baseline psychiatric assessment scores". No further details on the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Fluoxetine-treated patients received 20 mg of active drug in the morning and placebo in the evening. Desipramine-treated participants received 25 mg of active drug in the evening and placebo in the morning". The study is described as double-blind, however procedures for ensuring the blinding of who administered the intervention are not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The assessment was performed by the clinician, whose blindness is not discussed
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rate: 6 participants in the fluoxetine group (6/17, 35.3%) and 7 participants in the desipramine group (7/21, 33.3%). Number of participants and reasons for discontinuation are apparently balanced between the 2 groups. According to the text missing data were imputed, quote: "The endpoint analysis calculated changes from baseline [...] to the last observa-

Holland 1998 (*Continued*)

		tion carried forward...", however whether a proper ITT analysis was applied is unclear, since the number of analysed participants is not reported in the text or in the graphs
Selective reporting (reporting bias)	High risk	Outcomes are not clearly pre-specified (quote: "[...] our study prospectively examined the safety and efficacy of fluoxetine and desipramine in 40 depressed women [...]"). Outcomes of interest are poorly reported: neither mean scores on scales nor rates of remission are reported at any time point. The baseline-to-endpoint mean changes are represented in graphs, but not clearly reported in the text
Other bias	High risk	Quote: "This work was sponsored by Eli Lilly and Company". The role of funders in planning, conducting and writing the study is not discussed

Musselman 2006

Methods	6-week, randomised, double-blind, placebo-controlled, multicentre (2 centres), parallel-group study
Participants	Female outpatients aged 18 to 75 years with a current diagnosis of breast carcinoma (stage I-IV); DSM-III-R criteria for major depression or adjustment disorder with depressed mood for at least 2 months; score of at least 14 on the first 17 items of the 21-items HAM-D; last cancer treatment within the last 5 years
Interventions	Paroxetine: 13 participants. The dose was flexible, starting with 20 mg/day for the first 4 weeks, thereafter it could be increased at 40 mg/day Desipramine: 11 participants. The dose was flexible, starting with 25 mg/day and gradually titrated to 125 mg/day within the fourth week; thereafter it could be increased by 25 mg/day every 3 days up to 200 mg/day as the maximum dose Placebo: 11 participants
Outcomes	Efficacy and tolerability of paroxetine versus desipramine versus placebo in women with breast cancer, assessed with 21-item observer-rated Hamilton Rating Scale for Depression (HAM-D), 14-item observer-rated Hamilton Rating Scale for Anxiety (HAM-A), Clinical Global Impression Scale for Severity of Illness (CGI-S), routine adverse event monitoring and vital assessment for exploring tolerability. Quote: "The primary efficacy parameter was the mean change from baseline in the total score of the 21-item HAM-D. The secondary outcome measure was the mean change from baseline in the CGI-S score."
Notes	None

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients were then randomly assigned to one of the three double-blind treatment groups"; no further details on the sequence generation process. The 3 groups were similar for demographic and clinical features (with the exception of stage, being less advanced in the placebo-treated group, and previous chemotherapy, being less frequent in the placebo-treated group)
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is described as "double-blind", however procedures for ensuring the blinding of both participants and who administered the intervention are not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates: 5/13 (38.5%) participants in paroxetine group; 4/11 (36.4%) participants in desipramine group; 5/11 (45.4%) in placebo group. Reason for leaving the study are apparently balanced between groups, however dropout rates are relevant. Moreover, a relevant portion of missing data are possibly related to the true outcome (2 versus 2 versus 0 participants dropped due to inefficacy). Missing data were imputed. Quote: "Data are presented from the intention-to-treat population" and "the last-observation-carried-forward approach was applied for the missing data due to early dropout in the study."
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes are reported for the endpoint assessment (week 6)
Other bias	Unclear risk	3 authors report having received research support from several drug companies. Sponsorship bias cannot be ruled out since

		the funders of the study and their role in planning, conducting and writing it are not reported

Navari 2008

Methods	24-week, randomised, double-blind, placebo-controlled study
Participants	Women with early stage breast cancer (stages I, II) who were candidates for adjuvant hormonal therapy, local radiation and/or adjuvant chemotherapy treatment and had depressive symptoms, as indicated by a score of 2 or greater on the Two Question Screening Survey (TQSS). Participants who were "clinically depressed" were excluded
Interventions	Fluoxetine: number of participants not reported. The dose was 20 mg/day (not clearly reported if it was a fixed dose) Placebo: number of participants not reported
Outcomes	Efficacy of fluoxetine versus placebo on depressive symptoms (assessed with the 11-item Brief Zung Self-Rating Depression Scale - BZSDS), quality of life (assessed with the Functional Assessment of Cancer Therapy-General - FACT-G, version 3) and completion of adjuvant treatment. Quote: "The primary end points of the study were depressive symptoms, quality of life, and completion of adjuvant treatment."
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients with depressive symptoms were randomised to a daily oral antidepressant or a placebo"; no further details on the sequence generation process. Quote: "The groups were comparable at baseline in terms of age, disease distribution, performance status, and level of depressive symptoms". However, only the total number of randomised participants is reported, not the number of participants in each arm. Tables report results for 90 participants per arm
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is described as 'double-blind', however procedures for ensuring the blinding of both participants and who administered the intervention are not discussed

Navari 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	High risk	193 people were randomly assigned, but the number of participants for each arm is not reported. 180/193 (93%) participants completed the study. Dropout rates among the 2 groups and reasons for leaving the study early are not clearly reported. Missing data were not imputed and only participants who completed the study were analysed ('per protocol' analysis)
Selective reporting (reporting bias)	High risk	Results are reported only for subgroups (according to the type of adjuvant therapy assumed) not pre-specified. For relevant outcomes only results for "relevant improvement in depressive symptoms at 6 months" are reported, however how "significant improvement" is assessed is not clearly discussed
Other bias	Unclear risk	The Reich Family Endowment provided financial support for this investigation (not clearly reported if it is a private funder). The role of funders in planning, conducting and writing the study is not discussed

Pezzella 2001

Methods	8-week, multicentre (25 centres), double-blind, parallel-group, randomised study
Participants	Women, aged 18 to 65 years (actually, according to data reported in tables, older participants were also analysed), with a diagnosis of breast cancer (at any stage, but without cerebral metastases), with a rating of less than 2 on the World Health Organization (WHO) performance status scale and a life expectancy greater than 3 months; who had received chemotherapy and were scheduled to receive further cycles during the study period, and had received tamoxifen or paclitaxel and were scheduled to receive further treatment during the study. Participants had to be diagnosed with a mild, moderate or severe depressive episode, according to International Classification of Disease-10 (ICD-10) and have a score of greater than 16 on the Montgomery Åsberg Depression Rating Scale (MADRS). All participants gave written informed consent
Interventions	Paroxetine: 88 participants. Flexible dose, starting with 20 mg/day for the first 3 weeks. Thereafter the dose could be increased to 30 mg/day (after week 3) and to 40 mg/day (after week 5) if clinically indicated Amitriptyline: 87 participants. Flexible dose, titrating up to 75 mg/day within the first

	3 weeks. Thereafter the dose could be increased to 100 mg/day (after week 3) and to 150 mg/day (after week 5) if clinically indicated Placebo capsules were administered in order to maintain blindness
Outcomes	Quote: "[...] primary aim of comparing the efficacy and tolerability of paroxetine and amitriptyline in the treatment of depression in women with breast cancer". Efficacy was assessed with MADRS, CGI-S, Functional Living Index Cancer (FLIC) and patient's global evaluation (PGE) at endpoint. Tolerability was assessed by recording adverse events and evaluating vital signs and laboratory parameters
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "...a multicenter, double-blind, parallel-group, randomised study" and "...study participants [...] were randomly assigned in a ratio of 1:1 to 8-weeks treatment with either paroxetine [...] or amitriptyline [...]"; no further details on the sequence generation process. However, according to the tables, clinical and demographic features are similar between the 2 groups
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...a multicenter, double-blind, parallel-group, randomised study" and "a double-dummy technique was used to ensure blinding". Procedures for ensuring the blinding of who administered the intervention are not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates: 16/88 (18.2%) in the paroxetine group; 19/87 (21.8%) in the amitriptyline group. Side effects represent the most frequent reason for withdrawal (9 versus 10 participants). Other reasons are not discussed, however rates and reasons for losses are apparently balanced between groups. Imputations for missing data were performed. Quote: "Visitwise and endpoint statistical analyses were performed on

		the intent-to-treat (ITT) population (i.e. all participants who had taken at least one dose of study medication and who had at least one on-dose efficacy assessment). End-point analyses were constructed from week 8 observations, where available, and on a 'last observation carried forward' basis for participants who had discontinued study medication prematurely."
Selective reporting (reporting bias)	Unclear risk	Outcomes are not clearly pre-specified (quote: "[...] primary aim of comparing the efficacy and tolerability of paroxetine and amitriptyline [...]"), however key outcomes are reported as mean change scale scores at different time points
Other bias	Unclear risk	Sponsorship bias cannot be ruled out since a 'financial disclosure' is not reported

Razavi 1996

Methods	5-week, double-blind, placebo-controlled, randomised, multicentre trial (14 centres)
Participants	People (mostly females), aged over 18 years, diagnosed with an adjustment disorder (with a depressive mood or with mixed features) or from a major depressive disorder (excluding MDD with melancholic features) as defined by the DSM-III-R "in relation to" a cancer disease that had been diagnosed for a period of between 6 weeks and 7 years. Participants had to have a score of 13 or higher on the Hospital Anxiety and Depression Scale (HADS) before and after the 1-week period of placebo treatment, a rating of 60 or higher on the Karnofsky Performance Scale, and had to provide written informed consent
Interventions	Fluoxetine: 45 participants. The dose was 20 mg 1 tablet per day Placebo: 46 participants
Outcomes	Effectiveness and tolerance of fluoxetine versus placebo, assessed with the Hospital Anxiety and Depression Scale (HADS), Montgomery and Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAS), Revised Symptom Checklist (SCL90-R) and the Spitzer Quality of Life Index (SQOLI). The main assessment criterion was the success rate defined by a HADS score lower than 8 after 5 weeks of treatment. Treatment tolerance was assessed with AMDP5, weight, blood pressure, pulse, biochemical and haematological tests and spontaneous side effect reports
Notes	None
Risk of bias	

Razavi 1996 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was a double-blind, placebo-controlled, randomised, multicenter trial"; no further details on the sequence generation process. "The descriptive statistics for the baseline characteristics (demographic data and clinical variables) are comparable in the two treatment arms, except for delay since diagnosis, which was longer in the PA [placebo] group than in the FA [fluoxetine] group for randomised participants (P value = 0.03)."
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study is described as "double-blind", however procedures for ensuring the blinding of both participants and who administered the intervention are not discussed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rates: 15/45 (33.3%) participants in the fluoxetine group, 7/46 (15.2%) participants in the placebo group. Relevant rate particularly for the intervention group. There is imbalance between groups, however reasons for leaving the study early are described as apparently balanced between group. Quote: "Data analyses were performed [...] on an intent-to-treat basis on all randomised patients for the success rate, response rate and spontaneous side-effect reports. For evolution of assessment scales, analyses were performed on an intent-to-treat basis on patients who completed the study". However, only data for participants who completed the study have been analysed (according to a 'per protocol' analysis), and actually missing data were not imputed
Selective reporting (reporting bias)	Unclear risk	Outcomes are not clearly pre-specified (quote: "[...] evaluate, in a double-blind placebo-controlled design, the effectiveness of fluoxetine to treat and/or to control anx-

		iety and depression [...]"). For relevant outcomes mean scores on rating scales are reported for 'visit 1' (but it is not clearly explained if it matches with the baseline point) and for 'visit 5'
Other bias	High risk	Quote: "This study was supported by grants from Lilly France and Lilly Benelux". The role of funders in planning, conducting and writing the study is not discussed

Van Heeringen 1996

Methods	6-week, randomised, double-blind, placebo-controlled, single-centre study
Participants	Women over 18 years with breast cancer at stage I or II, without metastases, not qualifying for primary surgical treatment, treated with radiotherapy, and depression, diagnosed according to DSM-III criteria, and a score of at least 16 on the 21-item HDRS
Interventions	Mianserin: 28 participants. The dose was fixed at 30 mg/day for the first week and 60 mg/day thereafter Placebo: 27 participants
Outcomes	Efficacy and safety of mianserin versus placebo. Depression was assessed with the 21-item HRDS after 2, 4 and 6 weeks. Tolerability was assessed with the ROSE (Record of Symptoms Emerging) and clinical evaluation of vital signs and laboratory measurements
Notes	None

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "After baseline assessment [...] patients still satisfying entrance criteria were randomised to treatment with mianserin (M; n = 28) or placebo (P; n = 27)... " and "Both treatment groups were well matched regarding baseline characteristics. ..". No further details on the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Not discussed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "...a randomised, double-blind, placebo-controlled study" and "...mianserin (M; n = 28) or placebo (P; n = 27), which had been prepared as indistinguish-

Van Heeringen 1996 (*Continued*)

		able capsules and given as a single night-time dose". Not reported who was blinded (clinician, statistician, outcome assessor)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rates: mianserin group 6/28 (21. 4%); placebo group 15/27 (55.5%); 2 versus 11 due to inefficacy, 2 versus 4 due to side effects.The imbalance in total rates and in reasons for losses between groups is not discussed. This might have introduced bias, since dropouts in the placebo group mostly referred to inefficacy, which is likely related to the true outcome. Quote: "Efficacy analyses were performed on an intention to-treat basis, thus including the patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. Last observation carried forward (LOCF) analysis was performed at each assessment point, substituting missing values at all subsequent assessments by the last available value". Actually not all the randomised participants were analysed, but only those who received at least one dose of medication and had at least one assessment, which is closer to an 'as treated' analysis
Selective reporting (reporting bias)	Unclear risk	Outcomes are not clearly pre-specified (quote: "The aim of our study was to evaluate the efficacy and safety of mianserin in patients with breast cancer [...]"). However, mean change scores on HDRS, response rates and rates of relevant adverse events are reported
Other bias	High risk	Quote: "This study was supported by a grant from NV Organon, Oss, The Netherlands". The role of funders in planning, conducting and writing the study is not discussed

BZSDS: Brief Zung Self-Rating Depression Scale
CDT: Carbohydrate-deficient transferrin
CGI: Clinical Global Impression scale

CGI-I/CGI-S: Clinical Global Impression Scale for Severity of Illness
CO: test for diffusing capacity for carbon monoxide
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders - III - Revision
EI: Efficacy Index
EORTC: European Organisation for Research and Treatment of Cancer
HADS: Hospital Anxiety and Depression Scale
HAM-D: Hamilton Depression Rating Scale
HRSD: Hamilton Rating Scale for Depression
ITT: intention-to-treat
LOCF: last observation carried forward
MADRS: Montgomery Åsberg Depression Rating Scale
MDD: major depressive disorder
ZSRDS: Zung Self-Rating Depression Scale

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

Study	Reason for exclusion
Amodeo 2012	Not a relevant comparison group: participants in the 2 arms received the same drug at different doses
Biglia 2005	Wrong design: not randomised
Biglia 2009	Not a relevant comparison group: control group without placebo
Boekhout 2011	Not a relevant diagnostic status: participants not depressed when recruited
Caldera 2009	Wrong design: not randomised
Cankurtaran 2008	Participants with panic disorder and generalised anxious disorder were also enrolled
Capuron 2002	Not a relevant diagnostic status: participants not depressed when recruited
Capuron 2003	Not a relevant diagnostic status: participants not depressed when recruited
Del Carmen 1990	Not a relevant diagnostic status: participants not depressed when recruited
Ell 2010	Wrong design. This is a review and it refers to 3 studies, none of which are eligible
Evans 1988	Wrong design: not randomised
Heras 2013	Not a relevant diagnostic status: participants not depressed when recruited
Hua 2009	Not a relevant comparison group: control group without placebo
ISRCTN51232664	Study eligible according to the protocol, however no published or unpublished data were retrieved. We contacted the authors and they stated that the study never started due to concerns around drug interactions and cancer symptoms. No further clarifications were provided

(*Continued*)

JPRN-UMIN000003383	Wrong design: not randomised
Kalso 1996	Not a relevant diagnostic status: participants not depressed when recruited
Kamath 2010	Only the abstract of the study was available. Study eligible according to the abstract, but the author's feedback was negative: the study has been concluded due to recruitment issues
Kautio 2008	Not a relevant diagnostic status: participants not depressed when recruited
KCT0000076	Wrong design: not randomised
Kimmick 2006	Not a relevant diagnostic status: participants not depressed when recruited
Loibl 2007	Not a relevant diagnostic status (participants not depressed when recruited) and not a relevant comparison group
Lydiatt 2008	Not a relevant diagnostic status: participants not depressed when recruited
Marasanov 2013	Not a relevant diagnostic status (participants not depressed when recruited) and not a relevant comparison group
Morrow 2003	Not a relevant diagnostic status: participants not depressed when recruited
Musselman 2013	Not a relevant diagnostic status: participants not depressed when recruited
NCT00005805	Not a relevant diagnostic status: participants not depressed when recruited
NCT00129467	Not a relevant comparison group: the experimental arm received methylphenidate plus SSRI, the control arm received placebo plus SSRI
NCT00234195	Wrong design: not randomised
NCT00352885	Not a relevant diagnostic status: participants not depressed when recruited
NCT00488072	Not a relevant diagnostic status: participants not depressed when recruited
NCT00536172	Not a relevant diagnostic status: participants not depressed when recruited
NCT00832520	Not a relevant diagnostic status: participants not depressed when recruited
NCT01219673	Not a relevant diagnostic status: participants not depressed when recruited
NCT01256008	The study is eligible according to the protocol. We contacted the authors and they provided negative feedback; the design of the study has been changed and the antidepressant arm has been removed
NCT01501396	Not a relevant diagnostic status: participants not depressed when recruited

(*Continued*)

NCT01725048	Wrong design: not randomised
Ng 2014	Not a relevant comparison group: control group without placebo
Nunez 2013	Not a relevant diagnostic status: participants not depressed when recruited
Palesh 2012	Not a relevant diagnostic status: participants not depressed when recruited
Panerai 1990	Not a relevant diagnostic status: not only participants affected by cancer recruited
Rodriguez 2011	Not a relevant comparison group: control group without placebo
Roscoe 2005	Not a relevant diagnostic status: participants not depressed when recruited
Stockler 2007	Mixed population, also including participants with fatigue and anxious symptoms
Taraz 2013	Not a relevant diagnostic status: participants not affected by cancer
Theobald 2002	Not a relevant diagnostic status (participants not depressed when recruited) and not a relevant comparison group
Tondlova 1997	Wrong design: not randomised
Tondlova 2002	Not a relevant diagnostic status: participants not depressed when recruited
UKCCCR	Not a relevant diagnostic status: participants not depressed when recruited
Zhang 2003	Study described as "randomised", but the treatment received by the comparison arm is not clearly reported
Zhang 2011	Not a relevant comparison group: control group without placebo
Zvukova 2010	Not a relevant diagnostic status: participants with thyroid cancer and benign thyroid tumours were recruited, and not only depressed participants were recruited

SSRI: selective serotonin reuptake inhibitor

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

N0405078066

Methods	Randomised controlled trial
Participants	People with lung cancer
Interventions	Venlafaxine versus placebo
Outcomes	Effects on symptom profiles after 12 weeks (not clearly specified)
Notes	According to the protocol the study has been completed, but no published or unpublished data have been retrieved. Not clear if the study is eligible. Authors did not reply to our request for clarification and for data

NCT00066859

Methods	Randomised, double-blind study
Participants	Participants diagnosed with cancer (any site, any stage) and mild or moderate depression, according to HRSD score
Interventions	Sertraline versus St. John's Wort as active comparator
Outcomes	Change in depression severity as measured by Hamilton Depression Rating Scale at 4 months
Notes	The study is eligible according to the abstract, but results were not available. Authors did not reply to our request for data

NCT00387348

Methods	Interventional, randomised, double-blind study
Participants	Patients diagnosed with advanced lung or gastrointestinal cancer and major depressive disorder (according to DSM-IV and Endicott criteria). Age: 35 to 85 years
Interventions	Escitalopram versus placebo
Outcomes	Primary outcomes: response rate, defined as a 50% reduction in the Hamilton Depression Rating Scale (HAM-D) scores over 4 weeks; change in Hamilton Depression Rating Scale (HAM-D) scores at week 4
Notes	According to the protocol the study started in March 2006 and was supposed to be completed in April 2011. Results are not available. Authors did not reply to our request for data

UMIN000008768

Methods	Parallel, randomised, open-label study
Participants	Male and females with cancer, diagnosed with major depression; age greater than 20 years
Interventions	Mirtazapine versus duloxetine hydrochloride
Outcomes	Primary outcome: change in HAM-D scores between pretreatment baseline and 6-week treatment
Notes	The study is eligible according to the abstract, but results are not available. Authors did not reply to our request for data

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders - IV
HAM-D: Hamilton Depression Rating Scale
HRSD: Hamilton Rating Scale for Depression

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

NCT01598584

Trial name or title	Mirtazapine plus gemcitabine versus gemcitabine in metastasis pancreatic cancer
Methods	Parallel, randomised, double-blind study
Participants	People with pancreatic cancer and normal organic function such as liver function, cardiac function and renal function, and with definite depression and/or anxiety, measured with the Hamilton score (not further specified)
Interventions	Gemcitabine plus mirtazapine (up to 45 mg/die) versus gemcitabine plus placebo
Outcomes	Primary outcome: QoL evaluated by SF-36 scale. Secondary outcomes: anxiety and depression scores (not further specified), objective response rate, progression-free survival, overall survival and chemotherapy-induced nausea and vomiting
Starting date	June 2012
Contact information	Dr. Yi Ba; email address: zhoubaling123@163.com
Notes	Not clear if the study would be eligible: criteria for measuring depression at baseline are not clearly specified, nor the inclusion of people suffering from anxiety but not depression. The study is ongoing according to the author's feedback

QoL: quality of life

DATA AND ANALYSES

Comparison 1. Depression: efficacy as a continuous outcome at 6 to 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	5	266	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-1.01, 0.11]
1.1 SSRIs	4	194	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.50, 0.08]
1.2 Tricyclic antidepressants	1	17	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.95, 1.04]
1.3 Other antidepressants	1	55	Std. Mean Difference (IV, Random, 95% CI)	-1.77 [-2.40, -1.14]
2 Antidepressants versus antidepressants	3	237	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.34, 0.18]
2.1 Paroxetine versus desipramine	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.73, 0.88]
2.2 Paroxetine versus amitriptyline	1	175	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.46, 0.14]
2.3 Fluoxetine versus desipramine	1	38	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.45, 0.83]

Comparison 2. Depression: efficacy as a continuous outcome at 1 to 4 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	4	287	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-0.80, 0.20]
1.1 SSRIs	2	159	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.25, 0.37]
1.2 Other antidepressants	2	128	Std. Mean Difference (IV, Random, 95% CI)	-0.71 [-1.26, -0.16]

Comparison 3. Depression: efficacy as a dichotomous outcome at 6 to 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	5	417	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.62, 1.08]
1.1 SSRIs	3	272	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.11]
1.2 Tricyclic antidepressants	1	17	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.42, 2.86]
1.3 Other antidepressants	2	128	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.30, 0.75]
2 Antidepressants versus antidepressants	2	199	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.78, 1.53]
2.1 Paroxetine versus amitriptyline	1	175	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.79, 1.63]
2.2 Paroxetine versus desipramine	1	24	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.33, 2.18]

Comparison 4. Social adjustment at 6 to 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus antidepressants	1	175	Mean Difference (IV, Random, 95% CI)	0.10 [-0.38, 0.58]
1.1 Paroxetine versus amitriptyline	1	175	Mean Difference (IV, Random, 95% CI)	0.10 [-0.38, 0.58]

Comparison 5. Quality of life at 6 to 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	2	152	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.27, 0.37]
1.1 SSRIs	2	152	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.27, 0.37]
2 Antidepressants versus antidepressants	1	153	Mean Difference (IV, Random, 95% CI)	6.5 [0.21, 12.79]
2.1 Paroxetine versus amitriptyline	1	153	Mean Difference (IV, Random, 95% CI)	6.5 [0.21, 12.79]

Comparison 6. Acceptability (dropouts due to inefficacy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	6	455	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.13, 1.32]
1.1 SSRIs	4	310	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.10, 7.31]
1.2 Tricyclic antidepressants	1	17	Risk Ratio (M-H, Random, 95% CI)	2.92 [0.16, 52.47]
1.3 Other antidepressants	2	128	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.05, 0.65]
2 Antidepressants versus antidepressants	3	237	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.14, 5.06]
2.1 Fluoxetine versus desipramine	1	38	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Paroxetine versus amitriptyline	1	175	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Paroxetine versus desipramine	1	24	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.14, 5.06]

Comparison 7. Acceptability (dropouts due to side effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	6	455	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.52, 2.72]
1.1 SSRIs	4	310	Risk Ratio (M-H, Random, 95% CI)	2.20 [0.69, 6.98]
1.2 Tricyclic antidepressants	1	17	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.04, 7.25]
1.3 Other antidepressants	2	128	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.15, 2.35]
2 Antidepressants versus antidepressants	3	237	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.55, 1.99]
2.1 Fluoxetine versus desipramine	1	38	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.41, 3.62]
2.2 Paroxetine versus amitriptyline	1	175	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.38, 2.08]
2.3 Paroxetine versus desipramine	1	24	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.18, 16.25]

Comparison 8. Acceptability (dropouts due to any cause)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	6	455	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.49, 1.53]
1.1 SSRIs	4	310	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.93, 2.91]
1.2 Tricyclic antidepressants	1	17	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.24, 2.23]
1.3 Other antidepressants	2	128	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.25, 0.75]
2 Antidepressants versus antidepressants	3	237	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.53, 1.30]
2.1 Fluoxetine versus desipramine	1	38	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.29, 1.68]
2.2 Paroxetine versus amitriptyline	1	175	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.46, 1.51]
2.3 Paroxetine versus desipramine	1	24	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.37, 3.00]

Comparison 9. Subgroup analysis: psychiatric diagnosis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	4	197	Std. Mean Difference (IV, Random, 95% CI)	-0.51 [-1.23, 0.21]
1.1 Patients with major depressive disorder	2	90	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.94, 0.78]

1.2 Patients with adjustment disorder, dysthymic disorder, depressive symptoms	2	107	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.67, 0.10]
2 Antidepressants versus antidepressants	2	199	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
2.1 Patients with major depressive disorder	2	199	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
2.2 Patients with adjustment disorder, dysthymic disorder, depressive symptoms	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 10. Subgroup analysis: cancer site

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	5	266	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-1.01, 0.11]
1.1 Patients with breast cancer	2	90	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.94, 0.78]
1.2 Patients with other cancer types	3	176	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.54, 0.06]
2 Antidepressants versus antidepressants	3	237	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.34, 0.18]
2.1 Patients with breast cancer	2	199	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.41, 0.15]
2.2 Patients with other cancer types	1	38	Std. Mean Difference (IV, Random, 95% CI)	0.19 [-0.45, 0.83]

Comparison 11. Subgroup analysis: cancer stage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	2	93	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.66, 0.16]
1.1 Patients with an early stage cancer	1	69	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.65, 0.31]
1.2 Patients with a late stage cancer	1	24	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-1.30, 0.33]
2 Antidepressants versus antidepressants	1	38	Mean Difference (IV, Random, 95% CI)	0.69 [-1.61, 2.99]
2.1 Patients with an early stage cancer	1	38	Mean Difference (IV, Random, 95% CI)	0.69 [-1.61, 2.99]
2.2 Patients with a late stage cancer	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 12. Sensitivity analysis: excluding trials that did not employ depressive symptoms as their primary outcome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	4	183	Std. Mean Difference (IV, Random, 95% CI)	-0.49 [-1.23, 0.25]
1.1 SSRIs	3	111	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.58, 0.18]
1.2 Tricyclic antidepressants	1	17	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.95, 1.04]
1.3 Other antidepressants	1	55	Std. Mean Difference (IV, Random, 95% CI)	-1.77 [-2.40, -1.14]

Comparison 13. Sensitivity analysis: excluding trials with imputed data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antidepressants versus placebo	4	231	Std. Mean Difference (IV, Random, 95% CI)	-0.64 [-1.35, 0.06]
1.1 SSRIs	3	176	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.54, 0.06]
1.2 Tricyclic antidepressants	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Other antidepressants	1	55	Std. Mean Difference (IV, Random, 95% CI)	-1.77 [-2.40, -1.14]

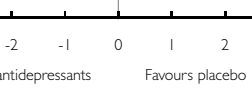
Analysis 1.1. Comparison 1 Depression: efficacy as a continuous outcome at 6 to 12 weeks, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 1 Depression: efficacy as a continuous outcome at 6 to 12 weeks

Outcome: 1 Antidepressants versus placebo

Study or subgroup	Antidepressant N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 SSRIs							
EUCTR2008-002159-25-FR	12	5.25 (4.45)	12	9.17 (10.15)		15.6 %	-0.48 [-1.30, 0.33]
Fisch 2003	38	21.14 (5.57)	45	22.54 (6.53)		20.3 %	-0.23 [-0.66, 0.21]
Musselman 2006	13	13.38 (5.66)	5	12.64 (4.99)		13.0 %	0.13 [-0.90, 1.16]
Razavi 1996	30	13.6 (7.2)	39	15 (8.8)		19.8 %	-0.17 [-0.65, 0.31]
Subtotal (95% CI)	**93**		**101**			**68.7 %**	**-0.21 [-0.50, 0.08]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.88$, df = 3 (P = 0.83); $I^2 = 0.0\%$							
Test for overall effect: Z = 1.44 (P = 0.15)							
2 Tricyclic antidepressants							
Musselman 2006	11	12.91 (6.16)	6	12.64 (4.99)		13.4 %	0.04 [-0.95, 1.04]
Subtotal (95% CI)	**11**		**6**			**13.4 %**	**0.04 [-0.95, 1.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.09 (P = 0.93)							
3 Other antidepressants							
Van Heeringen 1996	28	7.4 (3.6)	27	15.6 (5.4)		17.9 %	-1.77 [-2.40, -1.14]
Subtotal (95% CI)	**28**		**27**			**17.9 %**	**-1.77 [-2.40, -1.14]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.50 (P < 0.00001)							
Total (95% CI)	**132**		**134**			**100.0 %**	**-0.45 [-1.01, 0.11]**
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 21.30$, df = 5 (P = 0.00071); $I^2 = 77\%$							
Test for overall effect: Z = 1.57 (P = 0.12)							
Test for subgroup differences: $Chi^2 = 20.43$, df = 2 (P = 0.00), $I^2 = 90\%$							

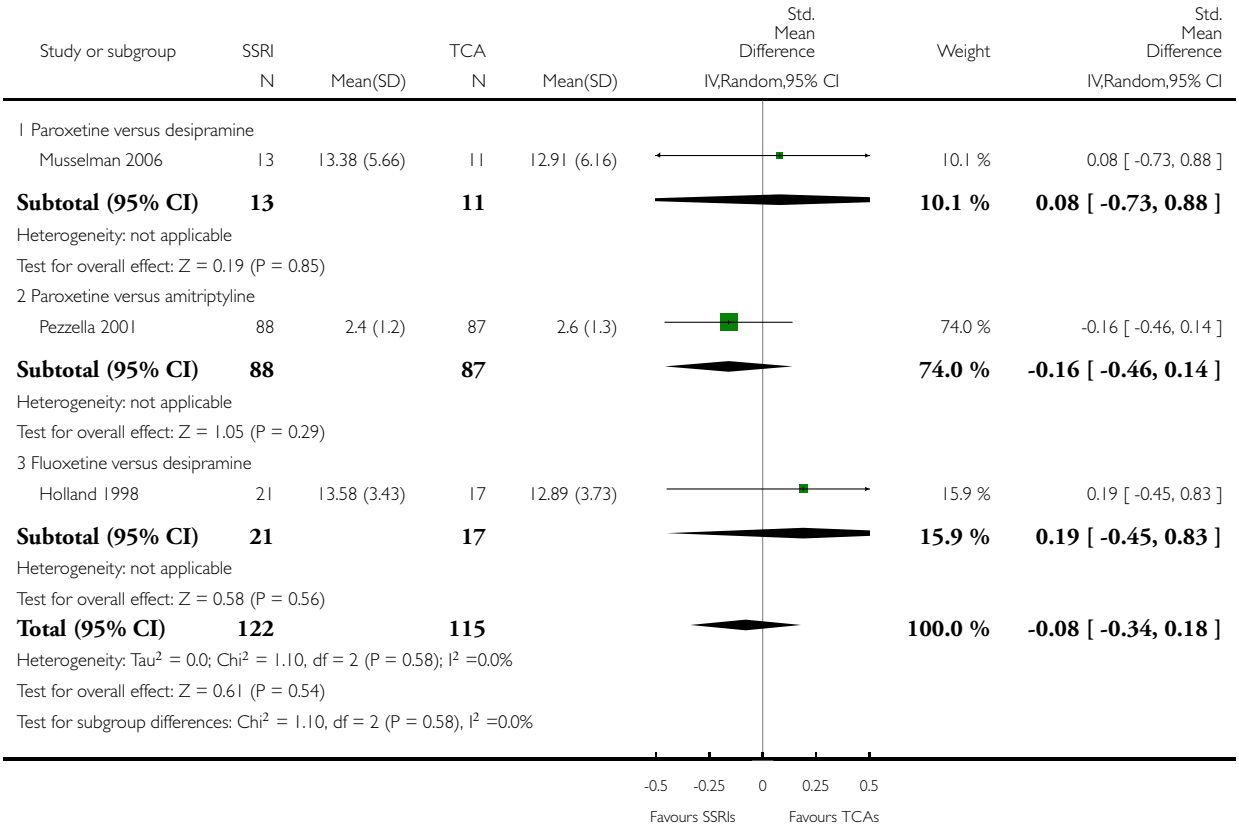


Analysis 1.2. Comparison 1 Depression: efficacy as a continuous outcome at 6 to 12 weeks, Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 1 Depression: efficacy as a continuous outcome at 6 to 12 weeks

Outcome: 2 Antidepressants versus antidepressants



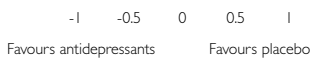
Analysis 2.1. Comparison 2 Depression: efficacy as a continuous outcome at 1 to 4 weeks, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 2 Depression: efficacy as a continuous outcome at 1 to 4 weeks

Outcome: 1 Antidepressants versus placebo

Study or subgroup	Antidepressant N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 SSRIs							
EUCTR2008-002159-25-FR	16	9.88 (6.83)	16	8.06 (6.38)		20.5 %	0.27 [-0.43, 0.96]
Fisch 2003	63	22.49 (6.06)	64	22.42 (5.63)		29.3 %	0.01 [-0.34, 0.36]
Subtotal (95% CI)	**79**		**80**			**49.8 %**	**0.06 [-0.25, 0.37]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.40 (P = 0.69)							
2 Other antidepressants							
Costa 1985	36	10.1 (5.58)	37	13.3 (8.09)		26.4 %	-0.45 [-0.92, 0.01]
Van Heeringen 1996	28	12.3 (3.6)	27	17 (5.4)		23.8 %	-1.01 [-1.58, -0.45]
Subtotal (95% CI)	**64**		**64**			**50.2 %**	**-0.71 [-1.26, -0.16]**
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 2.24$, df = 1 (P = 0.13); $I^2 = 55\%$							
Test for overall effect: Z = 2.55 (P = 0.011)							
Total (95% CI)	**143**		**144**			**100.0 %**	**-0.30 [-0.80, 0.20]**
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 12.08$, df = 3 (P = 0.01); $I^2 = 75\%$							
Test for overall effect: Z = 1.18 (P = 0.24)							
Test for subgroup differences: $Chi^2 = 5.82$, df = 1 (P = 0.02), $I^2 = 83\%$							

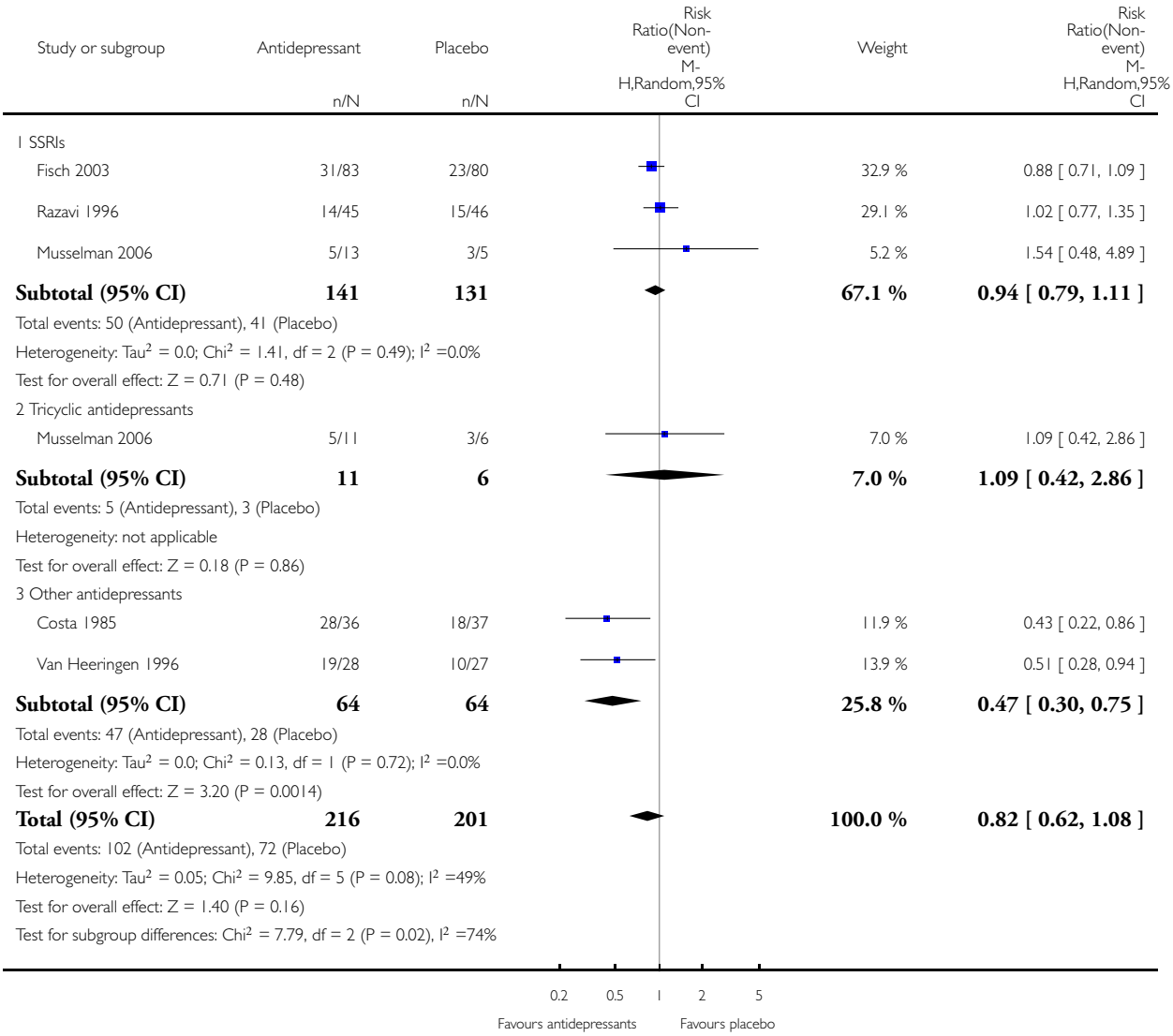


Analysis 3.1. Comparison 3 Depression: efficacy as a dichotomous outcome at 6 to 12 weeks, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 3 Depression: efficacy as a dichotomous outcome at 6 to 12 weeks

Outcome: 1 Antidepressants versus placebo

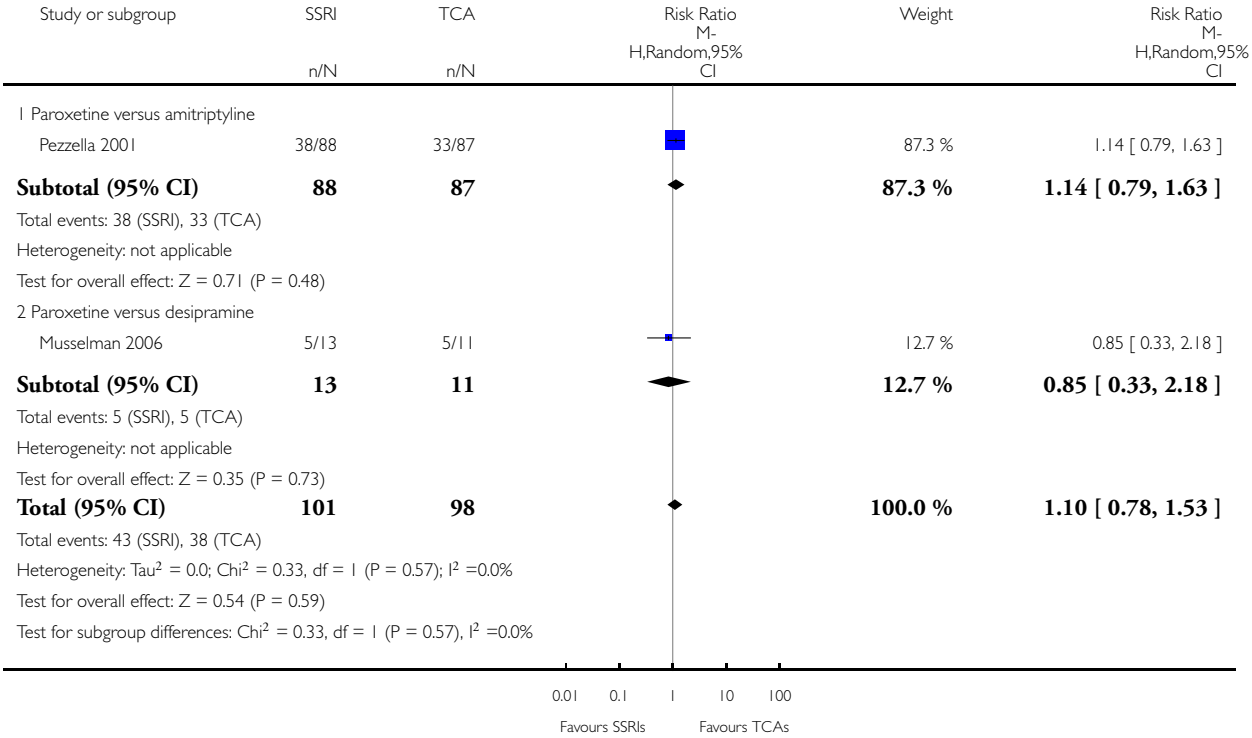


Analysis 3.2. Comparison 3 Depression: efficacy as a dichotomous outcome at 6 to 12 weeks, Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 3 Depression: efficacy as a dichotomous outcome at 6 to 12 weeks

Outcome: 2 Antidepressants versus antidepressants

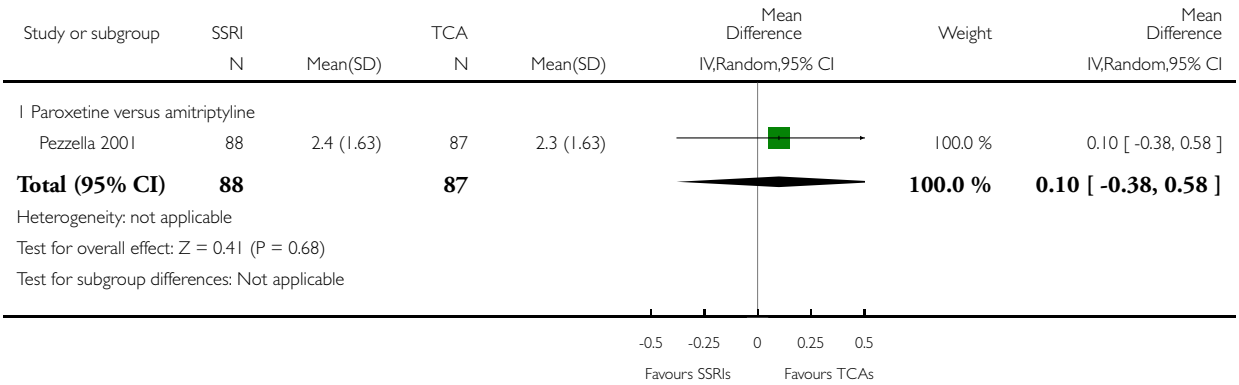


Analysis 4.1. Comparison 4 Social adjustment at 6 to 12 weeks, Outcome 1 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 4 Social adjustment at 6 to 12 weeks

Outcome: 1 Antidepressants versus antidepressants

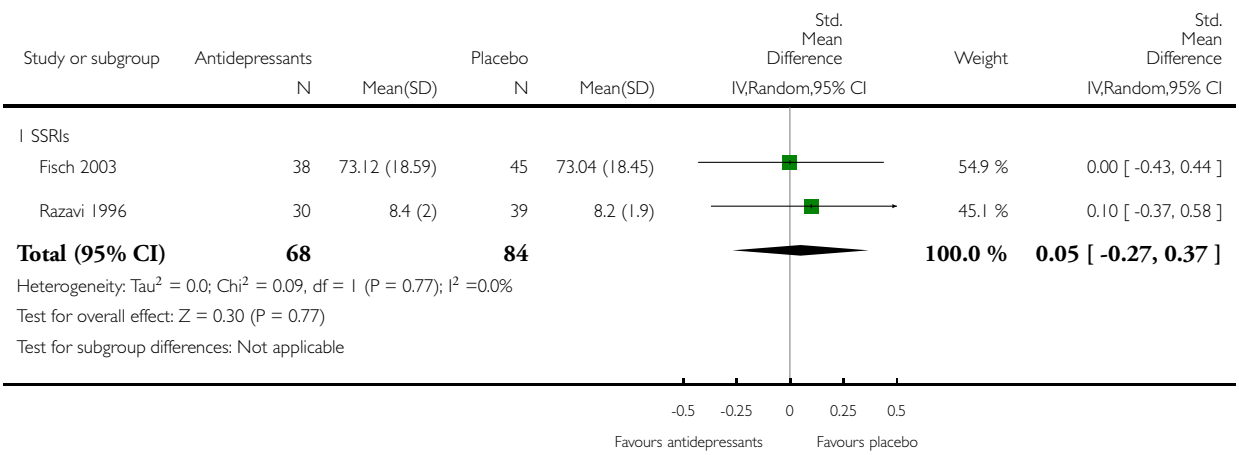


Analysis 5.1. Comparison 5 Quality of life at 6 to 12 weeks, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 5 Quality of life at 6 to 12 weeks

Outcome: 1 Antidepressants versus placebo

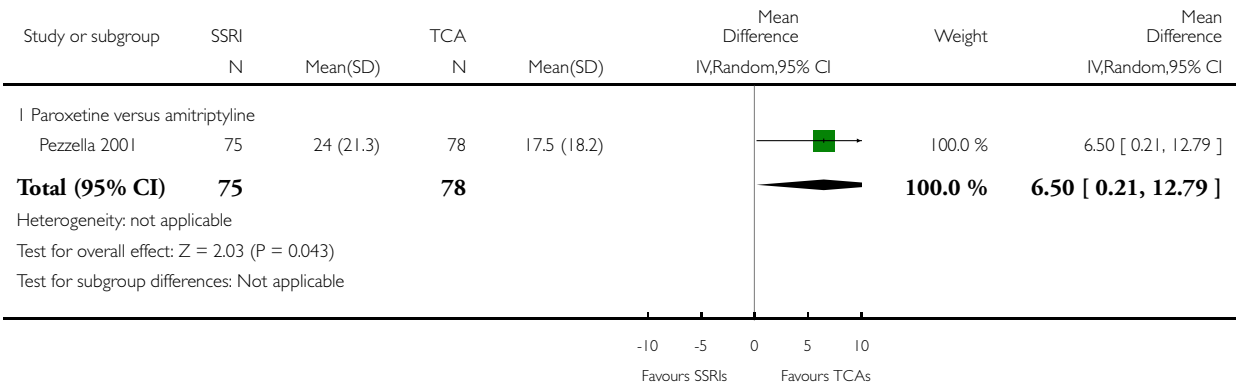


Analysis 5.2. Comparison 5 Quality of life at 6 to 12 weeks, Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 5 Quality of life at 6 to 12 weeks

Outcome: 2 Antidepressants versus antidepressants

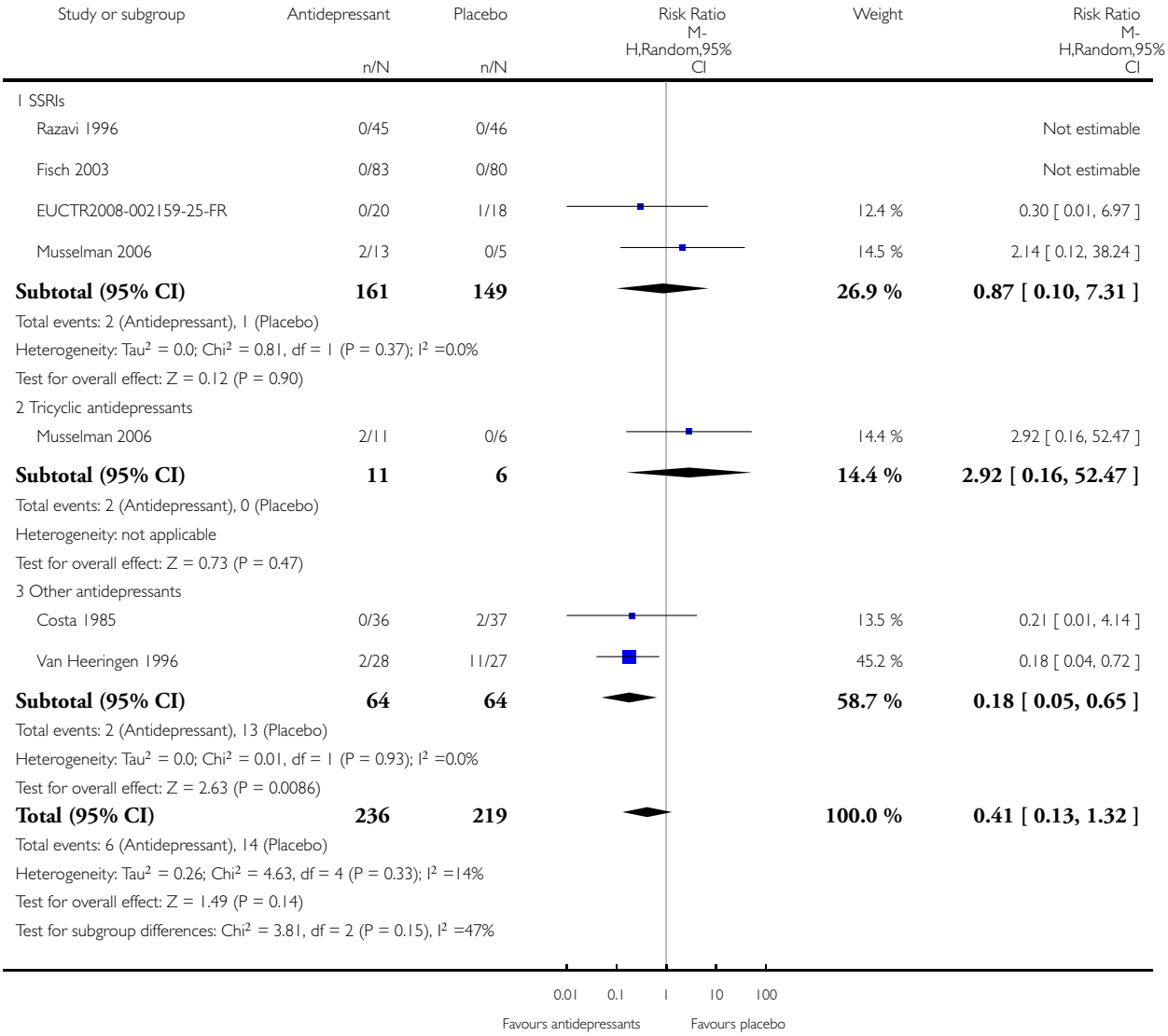


Analysis 6.1. Comparison 6 Acceptability (dropouts due to inefficacy), Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 6 Acceptability (dropouts due to inefficacy)

Outcome: 1 Antidepressants versus placebo



Analysis 6.2. Comparison 6 Acceptability (dropouts due to inefficacy), Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 6 Acceptability (dropouts due to inefficacy)

Outcome: 2 Antidepressants versus antidepressants

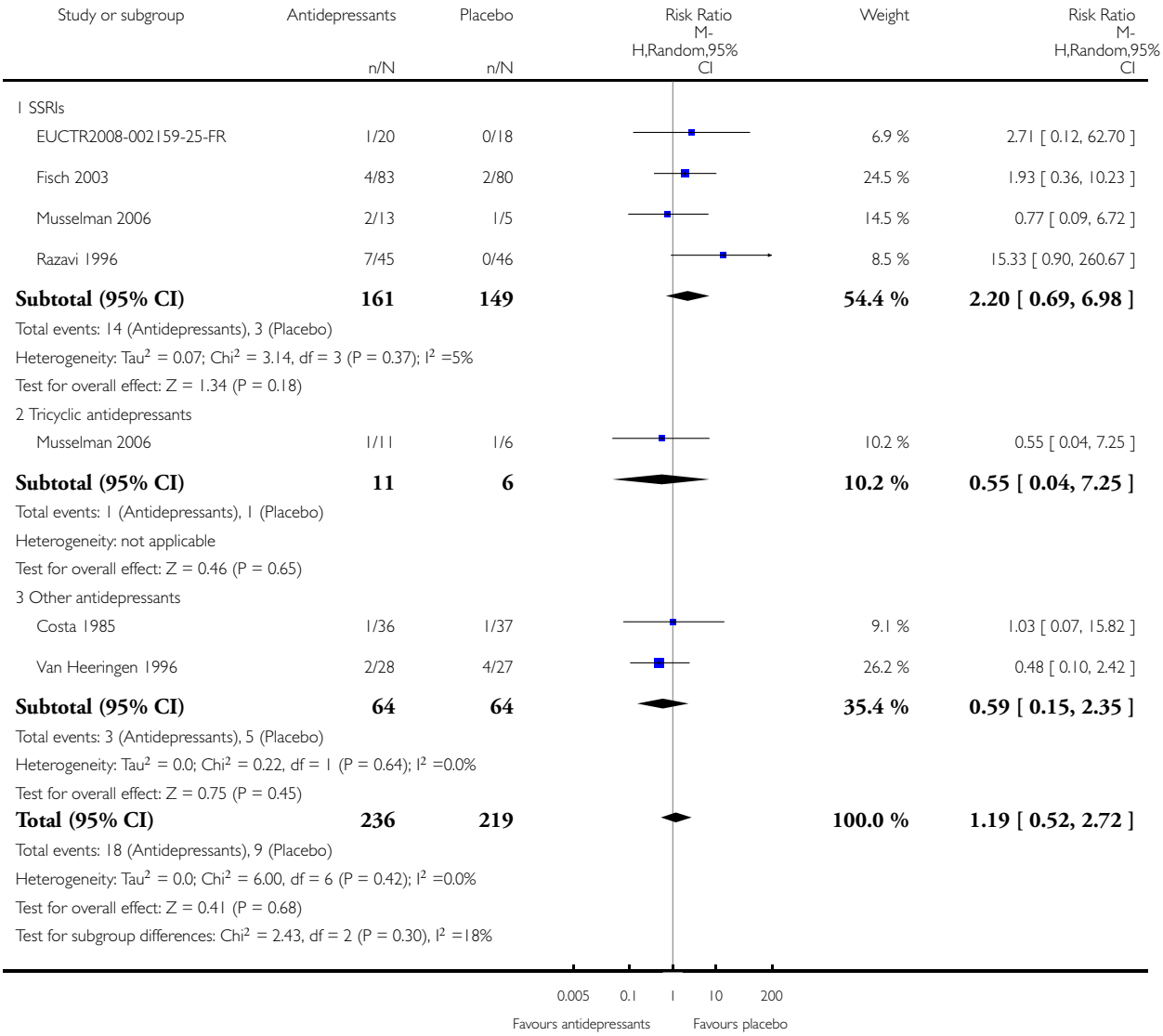
Study or subgroup	SSRI n/N	Tricyclic Antidepressant n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Fluoxetine versus desipramine					
Holland 1998	0/21	0/17			Not estimable
Subtotal (95% CI)	**21**	**17**			**Not estimable**
Total events: 0 (SSRI), 0 (Tricyclic Antidepressant)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Paroxetine versus amitriptyline					
Pezzella 2001	0/88	0/87			Not estimable
Subtotal (95% CI)	**88**	**87**			**Not estimable**
Total events: 0 (SSRI), 0 (Tricyclic Antidepressant)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Paroxetine versus desipramine					
Musselman 2006	2/13	2/11		100.0 %	0.85 [0.14, 5.06]
Subtotal (95% CI)	**13**	**11**		**100.0 %**	**0.85 [0.14, 5.06]**
Total events: 2 (SSRI), 2 (Tricyclic Antidepressant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.85)					
Total (95% CI)	**122**	**115**		**100.0 %**	**0.85 [0.14, 5.06]**
Total events: 2 (SSRI), 2 (Tricyclic Antidepressant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.85)					
Test for subgroup differences: Not applicable					

Analysis 7.1. Comparison 7 Acceptability (dropouts due to side effects), Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 7 Acceptability (dropouts due to side effects)

Outcome: 1 Antidepressants versus placebo

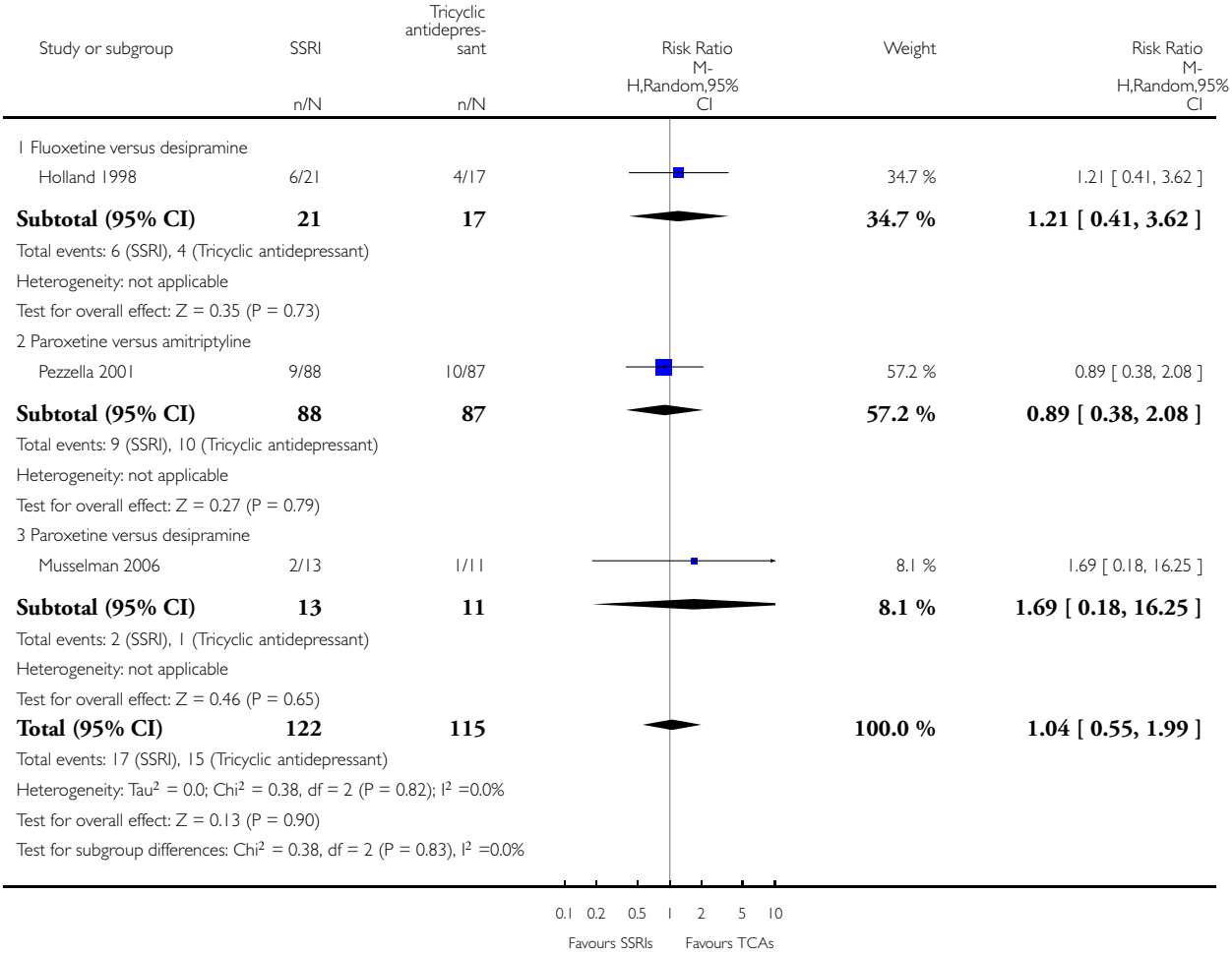


Analysis 7.2. Comparison 7 Acceptability (dropouts due to side effects), Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 7 Acceptability (dropouts due to side effects)

Outcome: 2 Antidepressants versus antidepressants

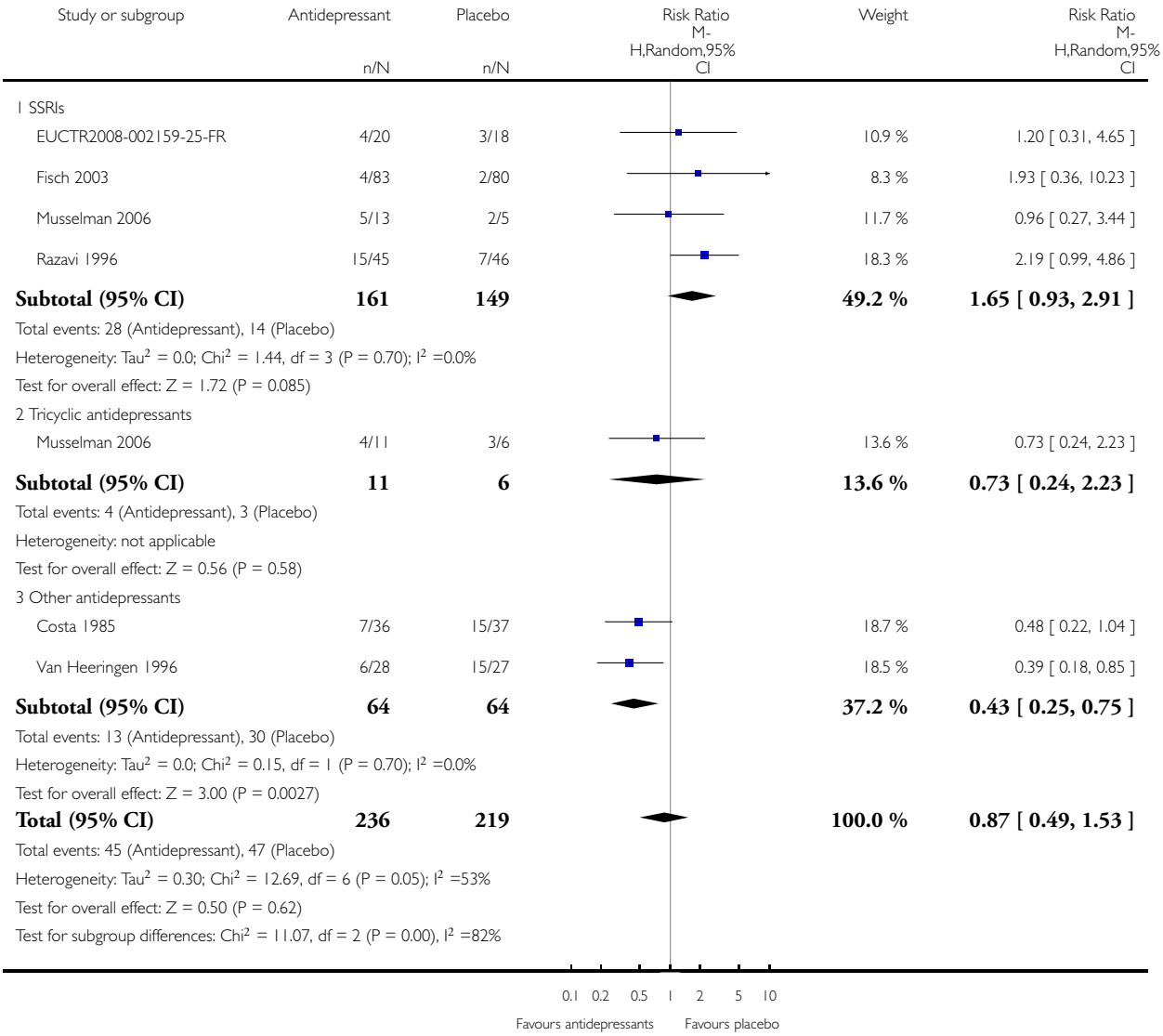


Analysis 8.1. Comparison 8 Acceptability (dropouts due to any cause), Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 8 Acceptability (dropouts due to any cause)

Outcome: 1 Antidepressants versus placebo

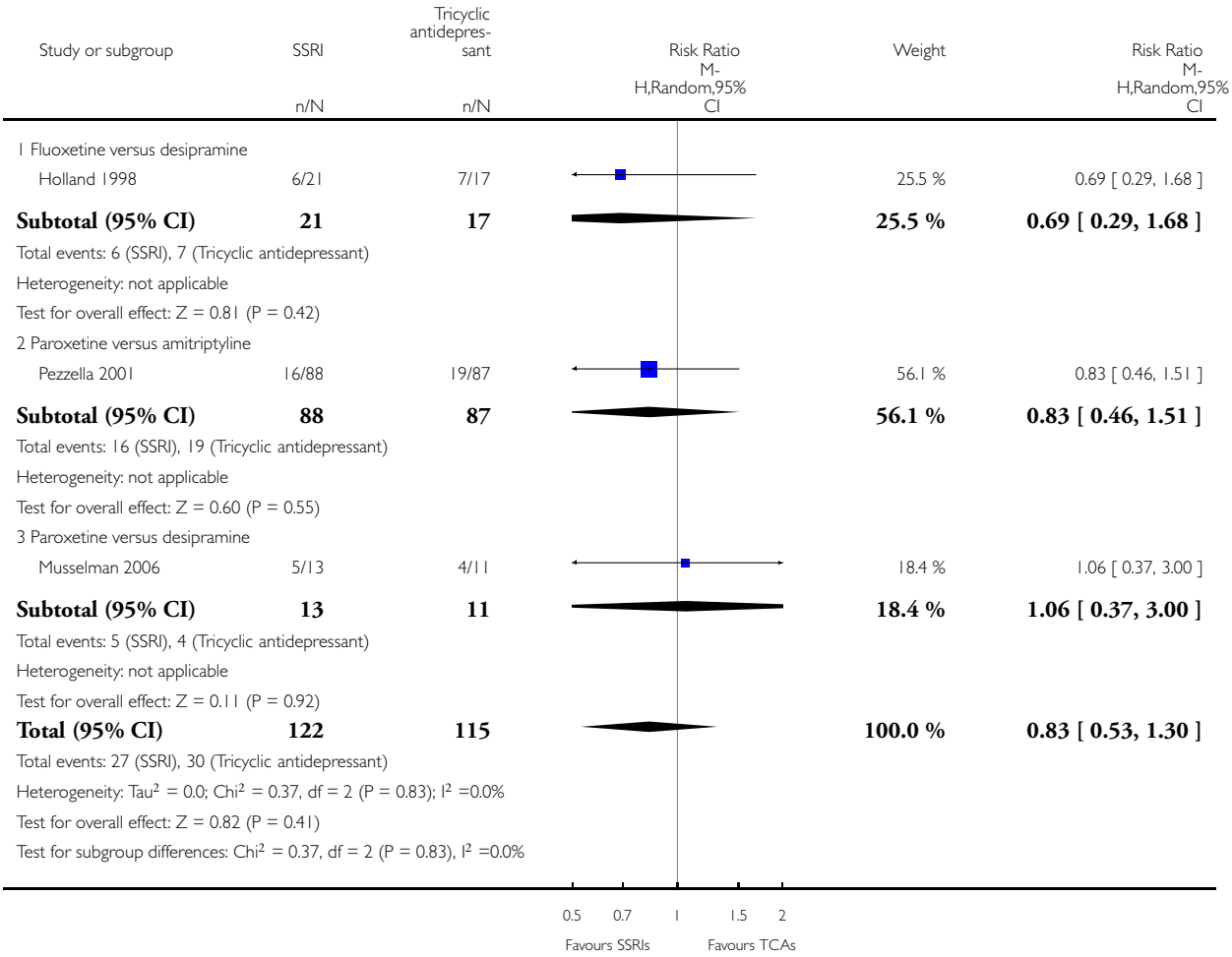


Analysis 8.2. Comparison 8 Acceptability (dropouts due to any cause), Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 8 Acceptability (dropouts due to any cause)

Outcome: 2 Antidepressants versus antidepressants

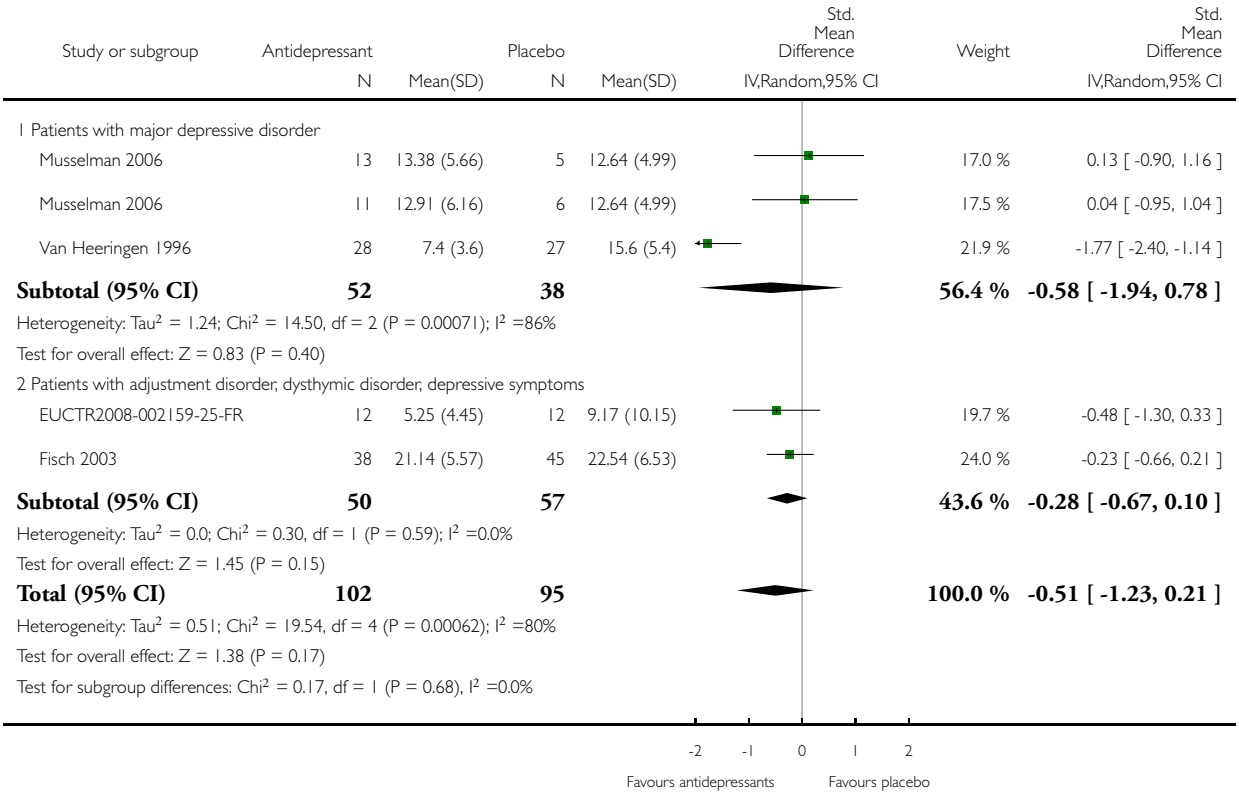


Analysis 9.1. Comparison 9 Subgroup analysis: psychiatric diagnosis, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 9 Subgroup analysis: psychiatric diagnosis

Outcome: 1 Antidepressants versus placebo

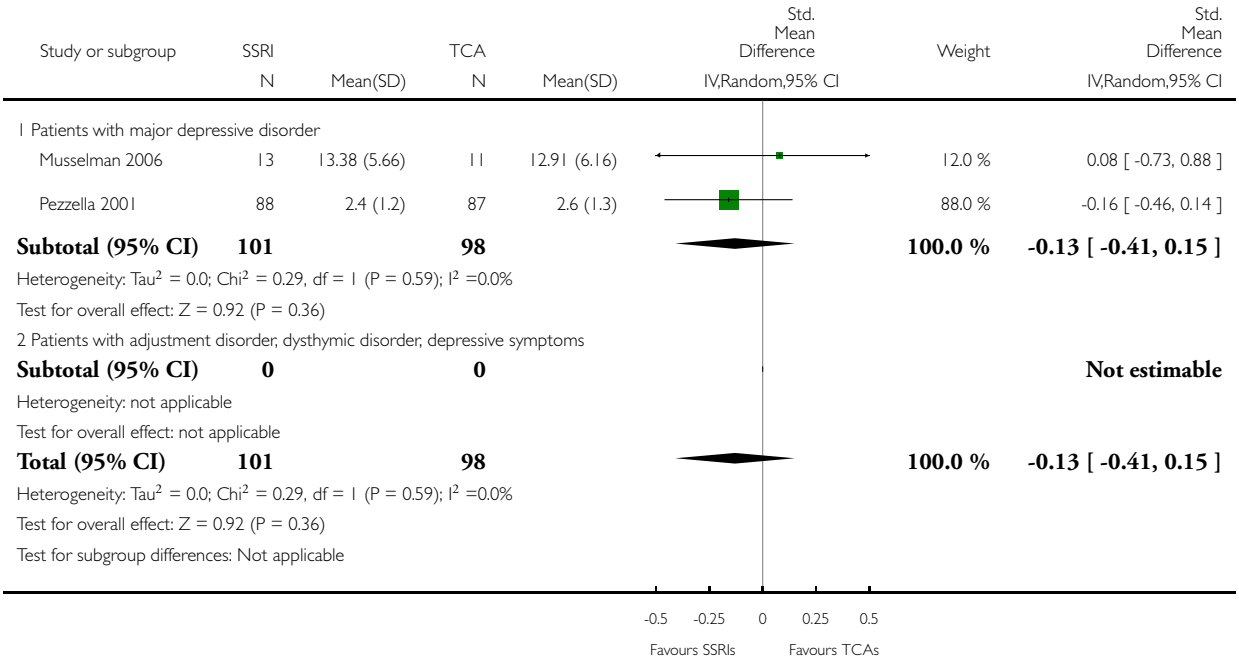


Analysis 9.2. Comparison 9 Subgroup analysis: psychiatric diagnosis, Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 9 Subgroup analysis: psychiatric diagnosis

Outcome: 2 Antidepressants versus antidepressants

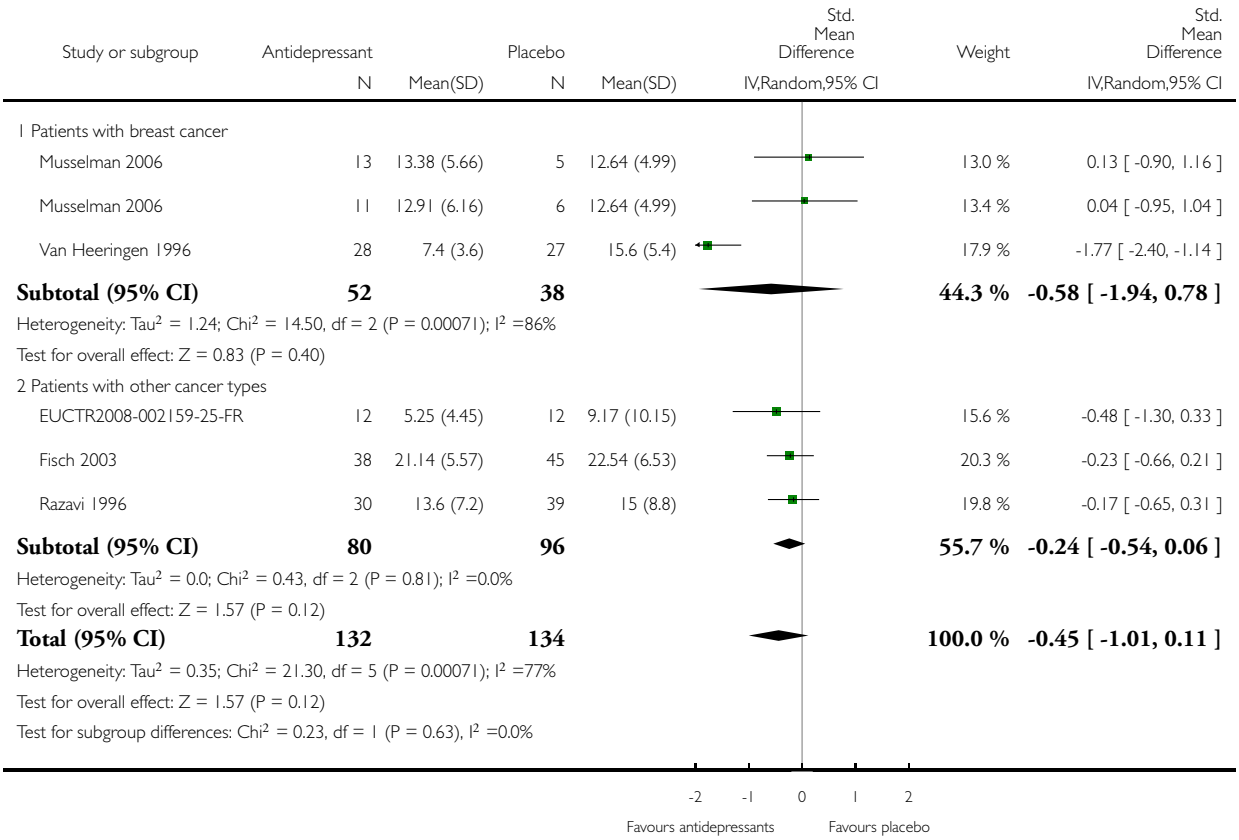


Analysis 10.1. Comparison 10 Subgroup analysis: cancer site, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 10 Subgroup analysis: cancer site

Outcome: 1 Antidepressants versus placebo

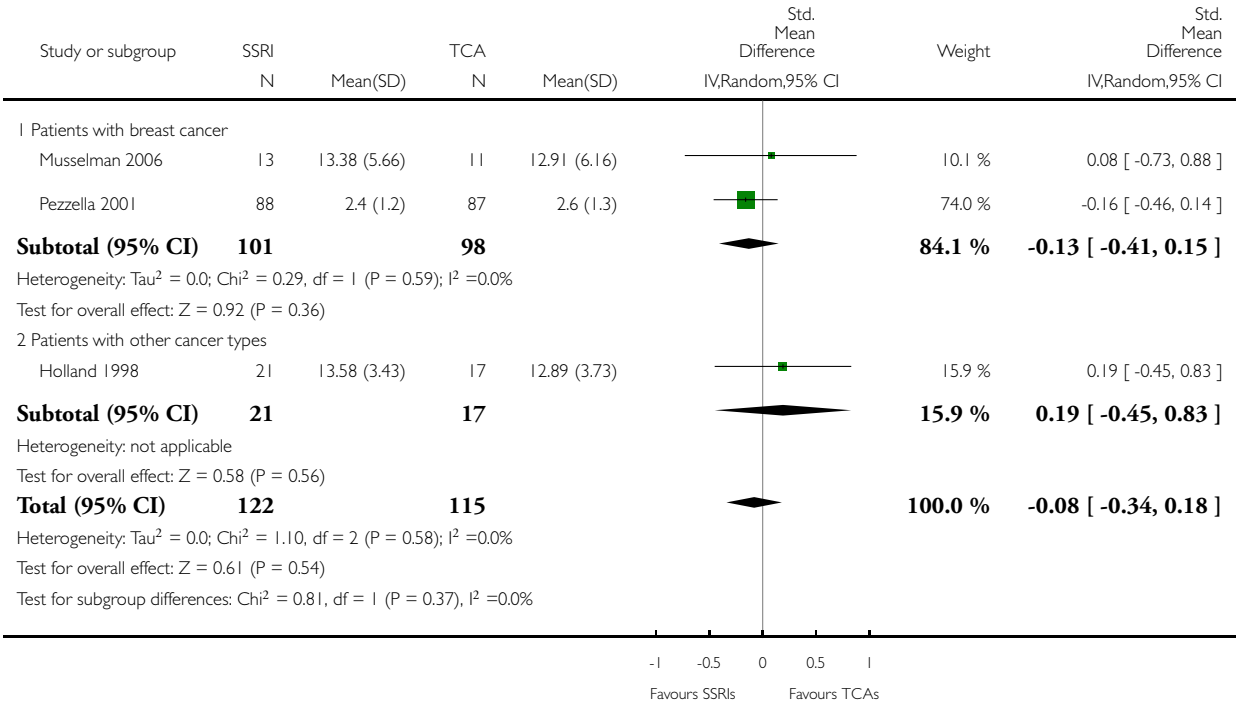


Analysis 10.2. Comparison 10 Subgroup analysis: cancer site, Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 10 Subgroup analysis: cancer site

Outcome: 2 Antidepressants versus antidepressants

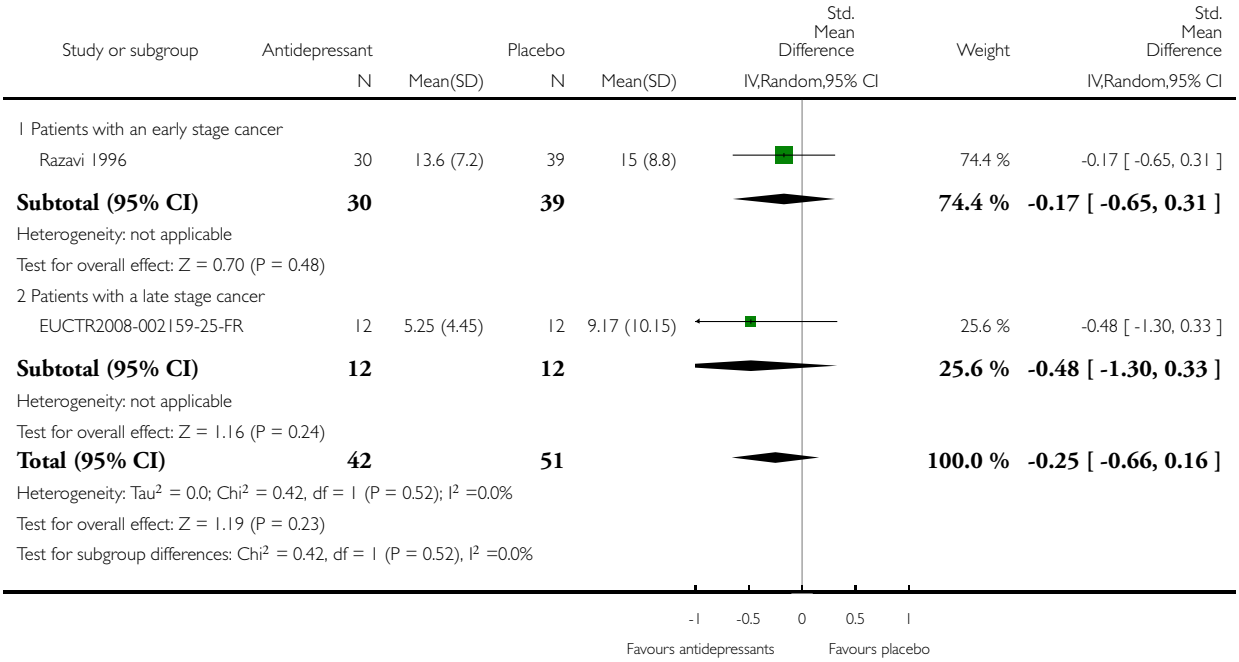


Analysis 11.1. Comparison 11 Subgroup analysis: cancer stage, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 11 Subgroup analysis: cancer stage

Outcome: 1 Antidepressants versus placebo



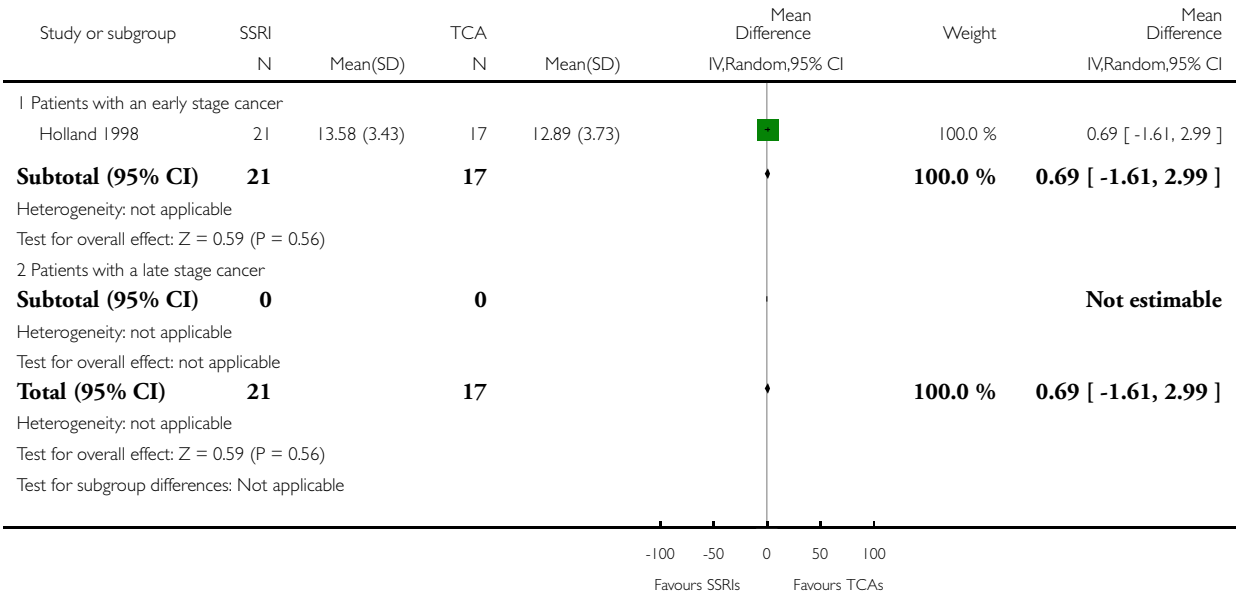
Analysis 11.2. Comparison 11 Subgroup analysis: cancer stage, Outcome 2 Antidepressants versus antidepressants.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 11 Subgroup analysis: cancer stage

Outcome: 2 Antidepressants versus antidepressants

Study or subgroup	SSRI N	Mean(SD)	TCA N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Patients with an early stage cancer							
Holland 1998	21	13.58 (3.43)	17	12.89 (3.73)		100.0 %	0.69 [-1.61, 2.99]
Subtotal (95% CI)	**21**		**17**			**100.0 %**	**0.69 [-1.61, 2.99]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.59 (P = 0.56)							
2 Patients with a late stage cancer							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Total (95% CI)	**21**		**17**			**100.0 %**	**0.69 [-1.61, 2.99]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.59 (P = 0.56)							
Test for subgroup differences: Not applicable							

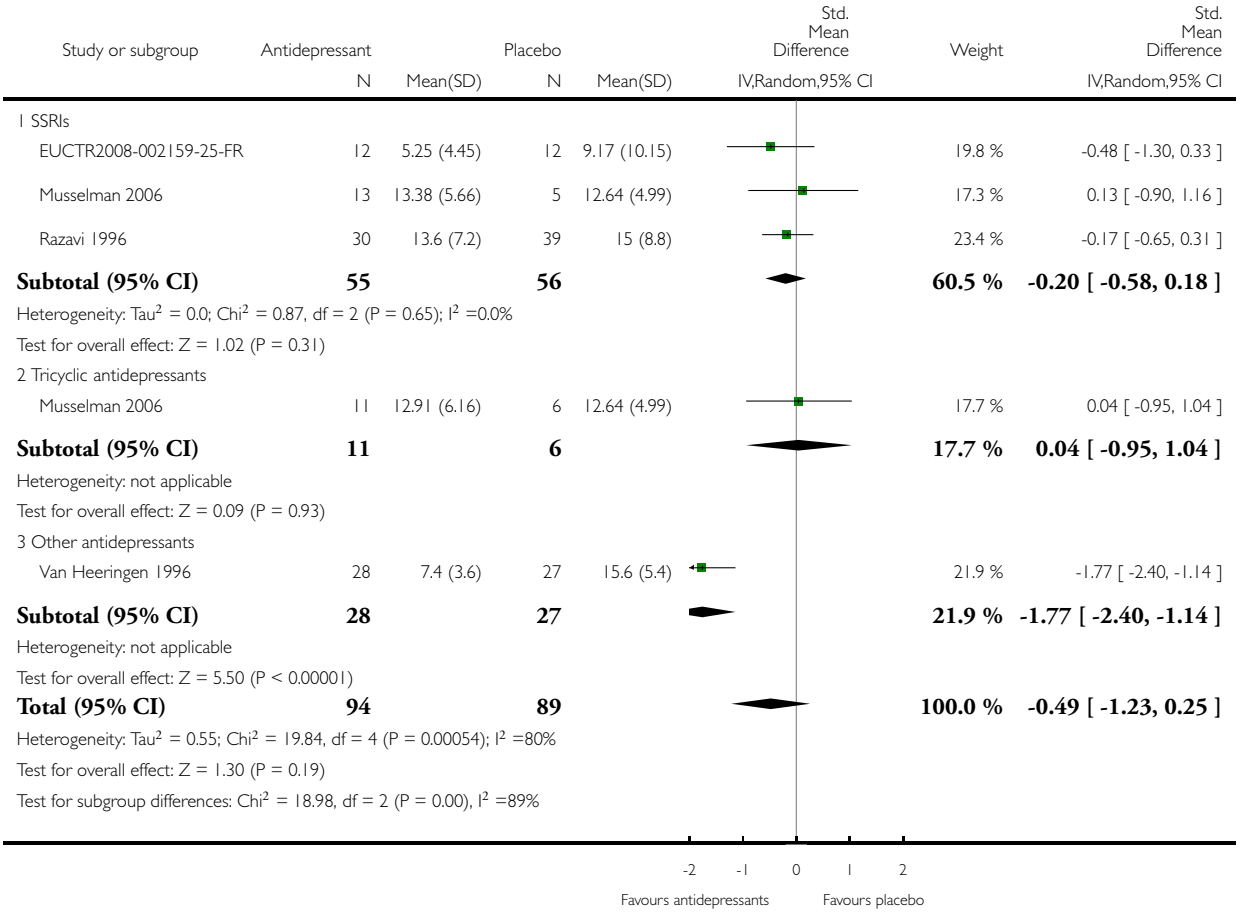


Analysis 12.1. Comparison 12 Sensitivity analysis: excluding trials that did not employ depressive symptoms as their primary outcome, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 12 Sensitivity analysis: excluding trials that did not employ depressive symptoms as their primary outcome

Outcome: 1 Antidepressants versus placebo

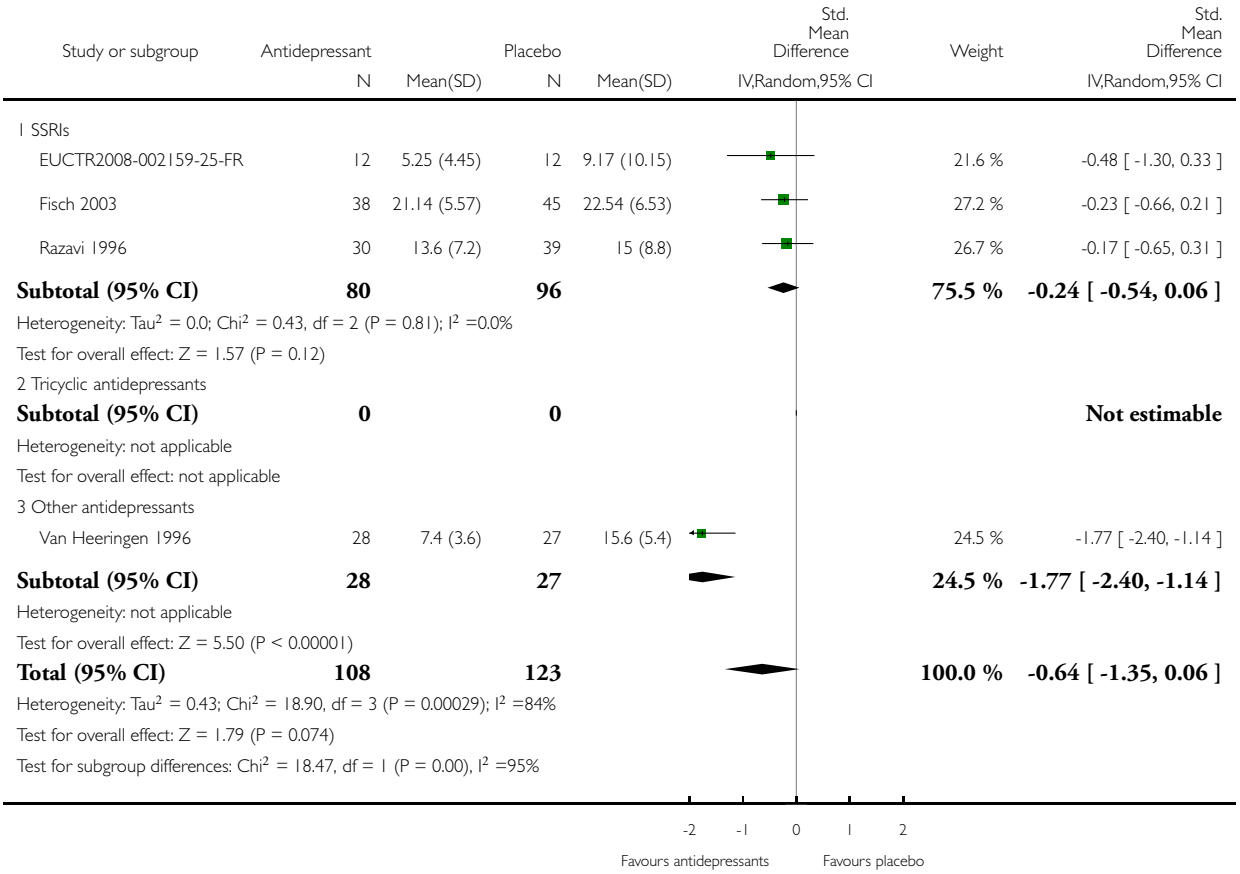


Analysis 13.1. Comparison 13 Sensitivity analysis: excluding trials with imputed data, Outcome 1 Antidepressants versus placebo.

Review: Antidepressants for the treatment of depression in people with cancer

Comparison: 13 Sensitivity analysis: excluding trials with imputed data

Outcome: 1 Antidepressants versus placebo



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Neoplasms] explode all trees
#2 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or choriocrcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*)
#3 #1 or #2
#4 MeSH descriptor: [Depression] explode all trees
#5 MeSH descriptor: [Depressive Disorder] explode all trees
#6 MeSH descriptor: [Adjustment Disorders] explode all trees
#7 (depress* or melanchol* or ((adjustment or reactive or dysthymic) near/5 disorder*))
#8 #4 or #5 or #6 or #7
#9 Any MeSH descriptor with qualifier(s): [Drug therapy - DT]
#10 MeSH descriptor: [Antidepressive Agents] explode all trees
#11 MeSH descriptor: [Heterocyclic Compounds] explode all trees
#12 MeSH descriptor: [Serotonin Uptake Inhibitors] explode all trees
#13 MeSH descriptor: [Adrenergic Uptake Inhibitors] explode all trees
#14 MeSH descriptor: [Monoamine Oxidase Inhibitors] explode all trees
#15 (desipramine or imipramine or clomipramine or opipramol or trimipramine or lofepramine or dibenzepin or amitriptyline or nortriptyline or protriptyline or doxepin or iprindole or melitracen or butriptyline or dosulepin or amoxapine or dimetacrine or amineptine or maprotiline or quinupramine or zimeldine or fluoxetine or citalopram or paroxetine or sertraline or alaproclate or fluvoxamine or etoperidone or escitalopram or isocarboxazid or nialamide or phenelzine or tranylcypromine or iproniazide or iproclozide or moclobemide or toloxatone or oxitriptan or tryptophan or mianserin or nomifensine or trazodone or nefazodone or minaprine or bifemelane or viloxazine or oxaflozane or mirtazapine or bupropion or medifoxamine or tianeptine or pivagabine or venlafaxine or milnacipran or reboxetine or gepirone or duloxetine or agomelatine or desvenlafaxine or vilazodone or hyperici herba or hypericum perforatum or st john* wort* or saint john* wort*)
#16 (anti-depress* or antidepress* or drug therap* or pharmacotherap* or trycyclic* or TCA* or heterocyclic* or serotonin uptake or SSRI* or SNRI* or monoamine oxidase inhibitor* or MAOI*)
#17 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #3 and #8 and #17

Appendix 2. MEDLINE search strategy

1 exp Neoplasms/
2 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or choriocarcinoma* or lymphoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*).mp.
3 1 or 2
4 Depression/
5 exp Depressive Disorder/
6 Adjustment Disorders/
7 (depress* or melanchol* or ((adjustment or reactive or dysthymic) adj5 disorder*)).mp.
8 4 or 5 or 6 or 7
9 drug therapy.fs.
10 exp Antidepressive Agents/
11 exp Heterocyclic Compounds/
12 exp Serotonin Uptake Inhibitors/
13 exp Adrenergic Uptake Inhibitors/
14 exp Monoamine Oxidase Inhibitors/
15 (anti-depress* or antidepress* or drug therap* or pharmacotherap* or trycyclic* or TCA* or heterocyclic* or serotonin uptake or SSRI* or SNRI* or monoamine oxidase inhibitor* or MAOI*).mp.
16 (desipramine or imipramine or clomipramine or opipramol or trimipramine or lofepramine or dibenzepin or amitriptyline or nortriptyline or protriptyline or doxepin or iprindole or melitracen or butriptyline or dosulepin or amoxapine or dimetacrine or

amineptine or maprotiline or quinupramine or zimeldine or fluoxetine or citalopram or paroxetine or sertraline or alaproclate or fluvoxamine or etoperidone or escitalopram or isocarboxazid or nialamide or phenelzine or tranylcypromine or iproniazide or iproclozide or moclobemide or toloxatone or oxitriptan or tryptophan or mianserin or nomifensine or trazodone or nefazodone or minaprine or bifemelane or viloxazine or oxaflozane or mirtazapine or bupropion or medifoxamine or tianeptine or pivagabine or venlafaxine or milnacipran or reboxetine or gepirone or duloxetine or agomelatine or desvenlafaxine or vilazodone or hyperici herba or hypericum perforatum or st john* wort* or saint john* wort*).mp.
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18 3 and 8 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 randomized.ab.
22 placebo.ab.
23 clinical trials as topic.sh.
24 randomly.ab.
25 trial.ti.
26 19 or 20 or 21 or 22 or 23 or 24 or 25
27 18 and 26
28 exp animals/ not humans.sh.
29 27 not 28
key:
mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier
pt = publication type
ab = abstract
sh = subject heading
ti = title

Appendix 3. EMBASE search strategy

1 exp neoplasm/
2 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or choriocrcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*).ti,ab.
3 1 or 2
4 exp depression/
5 adjustment disorder/
6 (depress* or melanchol* or ((adjustment or reactive or dysthymic) adj3 disorder*)).ti,ab.
7 4 or 5 or 6
8 exp antidepressant agent/
9 exp heterocyclic compound/
10 exp serotonin uptake inhibitor/
11 exp adrenergic receptor affecting agent/
12 exp monoamine oxidase inhibitor/
13 (anti-depress* or antidepress* or drug therap* or pharmacotherap* or trycyclic* or TCA* or heterocyclic* or serotonin uptake or SSRI* or SNRI* or monoamine oxidase inhibitor* or MAOI*).ti,ab.
14 (desipramine or imipramine or clomipramine or opipramol or trimipramine or lofepramine or dibenzepin or amitriptyline or nortriptyline or protriptyline or doxepin or iprindole or melitracen or butriptyline or dosulepin or amoxapine or dimetacrine or amineptine or maprotiline or quinupramine or zimeldine or fluoxetine or citalopram or paroxetine or sertraline or alaproclate or fluvoxamine or etoperidone or escitalopram or isocarboxazid or nialamide or phenelzine or tranylcypromine or iproniazide or iproclozide or moclobemide or toloxatone or oxitriptan or tryptophan or mianserin or nomifensine or trazodone or nefazodone or minaprine or bifemelane or viloxazine or oxaflozane or mirtazapine or bupropion or medifoxamine or tianeptine or pivagabine or venlafaxine or milnacipran or reboxetine or gepirone or duloxetine or agomelatine or desvenlafaxine or vilazodone or hyperici herba or hypericum perforatum or st john* wort* or saint john* wort*).ti,ab.

15 8 or 9 or 10 or 11 or 12 or 13 or 14
16 3 and 7 and 15
17 crossover procedure/
18 double-blind procedure/
19 randomized controlled trial/
20 single-blind procedure/
21 random*.mp.
22 factorial*.mp.
23 (crossover* or cross over* or cross-over*).mp.
24 placebo*.mp.
25 (double* adj blind*).mp.
26 (singl* adj blind*).mp.
27 assign*.mp.
28 allocat*.mp.
29 volunteer*.mp.
30 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
31 16 and 30
32 (exp animal/ or nonhuman/ or exp animal experiment/) not human/
33 31 not 32
key: [mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 4. PsycINFO search strategy

1 exp Neoplasms/
2 (cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma* or adenocarcinoma* or choriocrcinoma* or leukemia* or leukaemia* or metastat* or sarcoma* or teratoma*).ti,ab.
3 1 or 2
4 "depression (emotion)"/
5 exp major depression/
6 (depress* or melanchol* or ((adjustment or reactive or dysthymic) adj3 disorder*)).ti,ab.
7 4 or 5 or 6
8 exp antidepressant drugs/
9 exp neurotransmitter uptake inhibitors/
10 exp monoamine oxidase inhibitors/
11 exp Drug Therapy/
12 (anti-depress* or antidepress* or drug therap* or pharmacotherap* or trycyclic* or TCA* or heterocyclic* or serotonin uptake or SSRI* or SNRI* or monoamine oxidase inhibitor* or MAOI*).ti,ab.
13 (desipramine or imipramine or clomipramine or opipramol or trimipramine or lofepramine or dibenzepin or amitriptyline or nortriptyline or protriptyline or doxepin or iprindole or melitracen or butriptyline or dosulepin or amoxapine or dimetacrine or amineptine or maprotiline or quinupramine or zimeldine or fluoxetine or citalopram or paroxetine or sertraline or alaproclate or fluvoxamine or etoperidone or escitalopram or isocarboxazid or nialamide or phenelzine or tranylcypromine or iproniazide or iproclozide or moclobemide or toloxatone or oxitriptan or tryptophan or mianserin or nomifensine or trazodone or nefazodone or minaprine or bifemelane or viloxazine or oxaflozane or mirtazapine or bupropion or medifoxamine or tianeptine or pivagabine or venlafaxine or milnacipran or reboxetine or gepirone or duloxetine or agomelatine or desvenlafaxine or vilazodone or hyperici herba or hypericum perforatum or st john* wort* or saint john* wort*).ti,ab.
14 8 or 9 or 10 or 11 or 12 or 13
15 3 and 7 and 14
16 clinical trials/
17 (random* or trial* or group* or placebo*).ti,ab.
18 16 or 17
19 15 and 18

Appendix 5. Data collection sheet

Review author name (GO; FM; CB)
1. First author, Year and Journal ⋯⋯⋯⋯

2. Comparisons:
AD1 ⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯
AD2 ⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯
AD3 ⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯
PLB yes [ ] no [ ]

3. Weeks of follow-up |⋯||⋯| *(insert the longest duration of randomised follow-up)*

4. Randomisation |⋯| 0 = unclear
1 = clearly reported
authors' statement ⋯⋯⋯⋯
(If it is unclear please report the authors' statement)
5. Double blinding |⋯| 0 = unclear
1 = yes
2 = no
6. Concealment allocation |⋯|
0 = unclear
1 = yes *(clearly mentioned according to the Cochrane Handbook)*
7. AD1 sample |⋯||⋯||⋯| AD2 sample |⋯||⋯||⋯| AD3 sample |⋯||⋯||⋯| PLB sample |⋯||⋯||⋯|
(Please insert the number of patients randomised to receive each AD drug)
8. Setting |⋯|
0 = unclear 2 = outpatients 1 = inpatients 3 = in and outpatients
9. Type of participants |⋯|
0 = unclear 1 = major depressive disorder 3 = dysthymic disorder
2 = adjustment disorders 4 = depressive symptoms (rating scales)
'depression' definition (authors' statement) ⋯⋯⋯⋯
(If it is unclear please report the authors' statement)
10. Diagnostic criteria for 'depression' or depressive symptoms |⋯|
0 = unclear 3 = ICD-10, DSM-IV
1 = DSM-III 4 = rating scales (HRSD, BDI, etc.)
2 = DSM III-R 5 = implicit criteria (e.g. ICD-9)
diagnostic criteria (authors' statement) ⋯⋯⋯⋯⋯⋯
(If it is unclear please report the authors' statement)
11. Depressive symptoms employed as |⋯|
0 = primary trial outcome
1 = secondary trial outcome
12. Previous history of depression |⋯|
0 = exclusion criteria
1 = patients included N |⋯⋯⋯| % |⋯⋯⋯|
13. Elderly patients |⋯|
0 = unclear 2 = yes, some elderly (> 65 year old) patients
1 = no 3 = yes, all are 65 years old or older
14. Gender of patients
male |⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯| N |⋯⋯⋯| % |⋯⋯⋯|
female |⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯⋯| N |⋯⋯⋯| % |⋯⋯⋯|
15. Cancer site
(If the study includes a population with mixed cancer diagnosis, please insert the number and/or the percentage of patients for each site. If it is unclear please report the authors' statement)

site 1 |·····| N |·····| % |·····|
site 2 |·····| N |·····| % |·····|
site 3 |·····| N |·····| % |·····|
site 4 |·····| N |·····| % |·····|
site 5 |·····| N |·····| % |·····|
cancer site (authors' statement)·····
16. Cancer stage |·····|
(If the study includes a population with mixed cancer diagnosis, please insert the number and/or the percentage of patients for each stage. If it is unclear please report the authors' statement)
0 = unclear
1 = Stage 0 (carcinoma in situ; early form) N |·····| % |·····|
2 = Stage I (localised) N |·····| % |·····|
3 = Stage II (early locally advanced) N |·····| % |·····|
4 = Stage III (late locally advanced) N |·····| % |·····|
5 = Stage IV (metastasised) N |·····| % |·····|
cancer stage (authors' statement)·····
17. Cancer treatment |···|
(If the study includes a population with mixed cancer diagnosis, please insert the number and/or the percentage of patients for each treatment. If it is unclear please report the authors' statement)
0 = unclear
1 = chemotherapy N |·····| % |·····| 2 = radiotherapy N |·····| % |·····|
2 = surgery N |·····| % |·····|
3 = other treatment |·····| N |·····| % |·····|
cancer stage (authors' statement)·····
18. Severe adverse events
(if the type or the number of adverse events are not reported or are unclearly reported, please report the authors' statement)
1. ····· N |·····| % |·····|
2. ····· N |·····| % |·····|
3. ····· N |·····| % |·····|
4. ····· N |·····| % |·····|
adverse events (authors' statement)·····
19. Antidepressant (AD) doses
AD1 dose *METHODS |···||···||···| - |···||···||···| r = unclear
N.B. Is this a fixed or flexible dosing schedule? Fixed Flexible
** (Please consider the range of ID dose reported in the method section of the study report)*
**RESULTS |···||···||···| . |···||···| SD |···||···|.|···| r = unclear
N.B. Is this a mean dose? Yes No
*** (Please consider the average ID dose administered during the study period or, if this figure is not available, consider the average ID dose received by the majority of patients)*
D2 dose *METHODS |···||···||···| - |···||···||···| r = unclear
N.B. Is this a fixed or flexible dosing schedule? Fixed Flexible
**RESULTS |···||···||···| . |···||···| SD |···||···|.|···| r = unclear
N.B. Is this a mean dose? Yes No
AD3 dose *METHODS |···||···||···| - |···||···||···| r = unclear
N.B. Is this a fixed or flexible dosing schedule? Fixed Flexible
**RESULTS |···||···||···| . |···||···| SD |···||···|.|···| r = unclear
N.B. Is this a mean dose? Yes No
20. Mean score AT BASELINE: r = unclear/no data available
AD1
N |···||···||···| HDRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) ** Specify the N. of items in HDRS* |···||···|
N |···||···||···| MADRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| CGI |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)

N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(quality of life)*
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(social adjustment)*
AD2
N |···||···||···| HDRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| MADRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| CGI |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(quality of life)*
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(social adjustment)*
AD3
N |···||···||···| HDRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| MADRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| CGI |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(quality of life)*
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(social adjustment)*
PLACEBO
N |···||···||···| HDRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| MADRS |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| CGI |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(quality of life)*
N |···||···||···| ····· |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|) *(social adjustment)*

EFFICACY AS A CONTINUOUS OUTCOME

21**. ENDPOINT RESPONSE WEEK ….……** *(choose the time point given in the original study as the study endpoint)*
Mean score: r = unclear
Rating scale:······························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:······························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:······························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
(Please insert the number of evaluable subjects at follow-up, the mean score at follow-up at the HDRS or MADRS or CGI or any other rating scale. If the study used the LOCF, record the values based on the LOCF. If the SD is not available extract the standard error)
22. **1 to 4 weeks RESPONSE RATE WEEK ………** *(choose the time point closest to week 2)*
Mean score: r = unclear
Rating scale:······························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:······························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)

AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
(Please insert the number of evaluable subjects at follow-up, the mean score at follow-up at the HDRS or MADRS or CGI or any other rating scale. If the study used the LOCF, record the values based on the LOCF. If the SD is not available extract the standard error)
23**. 6 to 12 weeks RESPONSE RATE WEEK ....** *(choose the time point closest to the original study endpoint)*
Mean score: r = unclear
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
(Please insert the number of evaluable subjects at follow-up, the mean score at follow-up at the HDRS or MADRS or CGI or any other rating scale. If the study used the LOCF, record the values based on the LOCF. If the SD is not available extract the standard error)
24**. 14 to 24 weeks RESPONSE RATE WEEK ....** *(choose the time point closest to week 24)*
Mean score: r = unclear
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····························
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
(Please insert the number of evaluable subjects at follow-up, the mean score at follow-up at the HDRS or MADRS or CGI or any other rating scale. If the study used the LOCF, record the values based on the LOCF. If the SD is not available extract the standard error)
EFFICACY AS A DICHOTOMOUS OUTCOME
25.**ENDPOINT RESPONSE RATE (6 to 12 weeks) WEEK ....** *(choose the time point closest to the original study endpoint)*
50% or greater reduction on ···················
AD1 50% reduction RESPONDERS |···||···||···| out of |···||···||···| r = unclear
AD2 50% reduction RESPONDERS |···||···||···| out of |···||···||···|
AD3 50% reduction RESPONDERS |···||···||···| out of |···||···||···|

Placebo 50% reduction RESPONDERS |···||···||···| out of |···||···||···|
(Please insert which rating scale has been used, the number of patients with a 50% or more improvement - at the HAM-D, MADRS, or any other depression scale -, and the number of included patients at that time point. Typically, a trial would include N patients, but include N - p - q patients in the assessment, as these p patients have never returned and are hence excluded even from the LOCF analyses and q patients drop out in the course of the treatment and their last observed values are carried forward; in this instance, if q patients are somehow accounted for at the time point in question, then, N - p would be the denominator here. In some instances, only responders among N - p - q patients are reported.)
AD1 CGI-I RESPONDERS |···||···||···| out of |···||···||···| r = unclear
AD2 CGI-I RESPONDERS |···||···||···| out of |···||···||···|
AD3 CGI-I RESPONDERS |···||···||···| out of |···||···||···|
Placebo CGI-I RESPONDERS |···||···||···| out of |···||···||···|
(Please insert the number of patients 'much or very much improved' on CGI-Improvement, and the number of included patients at that time point.)
26. SOCIAL ADJUSTMENT (GAF and others) (6 to 12 weeks) WEEK …..…… *(choose the time point closest to the original study endpoint)*
Rating scale:·····
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)

27. HEALTH-RELATED QUALITY OF LIFE (6 to 12 weeks) WEEK …..…… *(choose the time point closest to the original study endpoint)*
(give preference to EORTC QLQ-30, FACT, SF-36 and other to illness-specific QoL scales, where available)
Rating scale:·····
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Rating scale:·····
AD1 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD2 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
AD3 N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)
Placebo N |···||···||···| score |···||···||···|.|···||···| SD |···|.|···||···| (SE |···|.|···||···|)

DROPOUT RATE

28. DROPOUTS = patient discontinuing the study before the end of follow-up r = unclear

Dropouts due to:	AD1 number	AD2 number	AD3 number	PLACEBO number
A - Inefficacy				
B - Side effects				
C - TOTAL*				

(*Continued*)

** The total number of dropout patients might not be the sum of dropouts for inefficacy and side effects, because in some studies patients drop out from the study for other/unknown reasons*
29. Cost analysis |˙˙˙|
0 = unclear
1 = yes
2 = no
30**.** Drug company sponsored trial |˙˙˙|
0 = unclear
1 = yes, sponsored by a drug company
2 = no
(A trial is judged 'drug company sponsored' if it is so declared in the conflict of interest or in the acknowledgment or if some of the authors are company employees. There may be other instances, and use your common sense)
31. NOTES

WHAT'S NEW

Last assessed as up-to-date: 28 April 2014.

Date	Event	Description
21 September 2016	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

GO, CB and MH planned the study. GO and FM retrieved and selected the studies, extracted the data and performed the quality assessment. GO and CB ran the analysis. GO drafted the manuscript, which was critically revised by FM, SD, CB and MH.

DECLARATIONS OF INTEREST

Giovanni Ostuzzi - nothing to declare

Faith Matcham - nothing to declare

Sarah Dauchy - nothing to declare

Corrado Barbui - nothing to declare

Matthew Hotopf - nothing to declare

SD conducted a multi-centre trial of participants with cancer and depressive symptoms that compared the efficacy of escitalopram versus placebo. This trial was supported financially by the Institut Gustave-Roussy and Lundbeck. To prevent bias the author was not involved in assessing the eligibility of the study, or in the extraction of data and quality assessment.

SOURCES OF SUPPORT

Internal sources

- Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Italy.

CB receives salary support from the University of Verona. GO is a Psychiatry trainee and receives salary support in the form of a public grant from the Italian Ministry of Health.

- Department of Psychological Medicine, The Institute of Psychiatry, King's College London, UK.

MH and FM receive salary support from the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

- Département Interdisciplinaire de Soins de Support, Gustave Roussy, France.

SD receives salary support from the Institute Gustave Roussy, Paris.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the Selection of studies paragraph to report that only the Endnote software was used.

In the paragraph Subgroup analysis and investigation of heterogeneity we clarified that the subgroup analyses were performed only for the primary outcome. We further specified which subgroups were considered.

We updated the section Description of the intervention with a brief discussion of a recent review and meta-analysis (Riblet 2014).

In the section Objectives we replaced the term 'people' with 'adults (18 years or older)'.

In the section Data extraction and management we made clear that the endpoint response rate and dropout rate were calculated on a strict intention-to-treat (ITT) basis.

In the section Measures of treatment effect we described which measures for the continuous and dichotomous outcomes were retrieved for the analyses. We moved the methodology for pooling these data from this section to the Data synthesis section, where we also specified the use of the Mantel-Haenszel methods for the analysis.

We moved the discussion on multiple intervention groups from the section Unit of analysis issues to the Data synthesis section.

In the Data synthesis section we removed the list of comparisons performed, namely antidepressants versus placebo and antidepressants versus antidepressants, as it was already reported in the paragraph Types of interventions. In this section we added a more detailed description on how data were managed and entered in the analysis, including the use of a random-effects model.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjustment Disorders [*drug therapy]; Antidepressive Agents [*therapeutic use]; Antidepressive Agents, Tricyclic [therapeutic use]; Depression [*drug therapy]; Depressive Disorder [*drug therapy]; Depressive Disorder, Major [drug therapy]; Dysthymic Disorder [drug therapy]; Neoplasms [*psychology]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [therapeutic use]

MeSH check words

Adult; Humans