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Duloxetine versus other anti-depressive agents for depression

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Abstract

Background—Although pharmacological and psychological interventions are both effective for major depression, in primary and secondary care settings antidepressant drugs remain the mainstay of treatment. Amongst antidepressants many different agents are available. Duloxetine hydrochloride is a dual reuptake inhibitor of serotonin and norepinephrine and has been licensed by the Food and Drug Administration in the US for major depressive disorder (MDD), generalised anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia and chronic musculoskeletal pain.

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CONTRIBUTIONS OF AUTHORS

AC, CB and TAF conceived and designed the meta-analysis. AC, MK, CT, MN, MP and IMO identified and acquired reports of trials, and extracted data. AC, MP, CT, MN and MK contacted authors of trials and pharmaceutical industries for additional information. AC and CB analysed and interpreted the data. TAF provided statistical advice and input. MK, IMO, CT, MN and MP contributed to the interpretation of the data. AC drafted the manuscript. CB, MK, MP, CT, MN, IMO and TAF critically reviewed the manuscript.

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NOTES This review is one of a number of separate reviews examining head to head comparisons as part of the multiple Meta-Analyses of New Generation Antidepressants (MANGA) Study. These individual reviews have been then combined in a multiple treatments meta-analysis (Cipriani 2009a).

Objectives—To assess the evidence for the efficacy, acceptability and tolerability of duloxetine in comparison with all other antidepressant agents in the acute-phase treatment of major depression.

Search methods—MEDLINE (1966 to 2012), EMBASE (1974 to 2012), the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register and the Cochrane Central Register of Controlled Trials up to March 2012. No language restriction was applied. Reference lists of relevant papers and previous systematic reviews were hand-searched. Pharmaceutical company marketing duloxetine and experts in this field were contacted for supplemental data.

Selection criteria—Randomised controlled trials allocating patients with major depression to duloxetine versus any other antidepressive agent.

Data collection and analysis—Two review authors independently extracted data and a double-entry procedure was employed. Information extracted included study characteristics, participant characteristics, intervention details and outcome measures in terms of efficacy, acceptability and tolerability.

Main results—A total of 16 randomised controlled trials (overall 5735 participants) were included in this systematic review. Of these, three trials were unpublished. We found 11 studies (overall 3304 participants) comparing duloxetine with one selective serotonin reuptake inhibitor (SSRI) (six studies versus paroxetine, three studies versus escitalopram and two versus fluoxetine), four studies (overall 1978 participants) comparing duloxetine with a newer antidepressant (three with venlafaxine and one with desvenlafaxine, respectively) and one study (overall 453 participants) comparing duloxetine with an antipsychotic drug which is also used as an antidepressive agent, quetiapine. No studies were found comparing duloxetine with tricyclic antidepressants. The pooled confidence intervals were rather wide and there were no statistically significant differences in efficacy when comparing duloxetine with other antidepressants. However, when compared with escitalopram or venlafaxine, there was a higher rate of drop out due to any cause in the patients randomised to duloxetine (odds ratio (OR) 1.62; 95% confidence interval (CI) 1.01 to 2.62 and OR 1.56; 95% CI 1.14 to 2.15, respectively). There was also some weak evidence suggesting that patients taking duloxetine experienced more adverse events than paroxetine (OR 1.24; 95% CI 0.99 to 1.55).

Authors' conclusions—Duloxetine did not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute-phase treatment of major depression. No differences in terms of efficacy were found, even though duloxetine was worse than some SSRIs (most of all, escitalopram) and newer antidepressants (like venlafaxine) in terms of acceptability and tolerability. Unfortunately, we only found evidence comparing duloxetine with a handful of other active antidepressive agents and only a few trials per comparison were found (in some cases we retrieved just one trial). This limited the power of the review to detect moderate, but clinically meaningful differences between the drugs. As many statistical tests have been used in the review, the findings from this review are better thought of as hypothesis forming rather than hypothesis testing and it would be very comforting to see the conclusions replicated in future trials. Most of included studies were sponsored by the drug industry manufacturing duloxetine. As for all other new investigational compounds, the potential for overestimation of treatment effect due to sponsorship bias should be borne in mind. In the present review no trials reported economic

outcomes. Given that several SSRIs and the great majority of antidepressants are now available as generic formulation (only escitalopram, desvenlafaxine and duloxetine are still on patent), more comprehensive economic estimates of antidepressant treatment effect should be considered to better inform healthcare policy.

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Citalopram [therapeutic use]; Cyclohexanols [therapeutic use]; Depression [drug therapy]; Dibenzothiazepines [therapeutic use]; Fluoxetine [therapeutic use]; Paroxetine [therapeutic use]; Randomized Controlled Trials as Topic; Thiophenes [*therapeutic use]

MeSH check words

Humans

BACKGROUND

Description of the condition

Major depression is generally diagnosed when a persistent and un-reactive low mood and loss of all interest and pleasure are accompanied by a range of symptoms including appetite loss, insomnia, fatigue, loss of energy, poor concentration, psychomotor symptoms, inappropriate guilt and morbid thoughts of death (APA 1994). It was the third leading cause of burden among all diseases in the year 2002, and it is expected to show a rising trend during the coming 20 years (WHO 2006). This condition is associated with marked personal, social and economic morbidity, loss of functioning and productivity, and creates significant demands on service providers in terms of workload (NICE 2010).

Description of the intervention

Duloxetine hydrochloride is structurally different from the tri-cyclic antidepressants (TCAs), heterocyclics, and also differs chemically from selective serotonin reuptake inhibitors (SSRIs). It is a potent dual reuptake inhibitor of serotonin and norepinephrine (Bymaster 2001), but lacks significant affinity for muscarinic, histaminergic, -adrenergic, dopaminergic, serotonergic, and opioid receptors (Wong 2002). Duloxetine has been licensed by the Food and Drug Administration (FDA) in the US for major depressive disorder (MDD), generalised anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia and chronic musculoskeletal pain. Duloxetine has an elimination half-life of about 12 hours (range 10 to 15 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Elimination of duloxetine is mainly through hepatic metabolism.

How the intervention might work

Dysregulation within central monoaminergic systems was believed to underlie the pathology of depression. However, recent evidence indicates that problems in information processing within neural networks, rather than changes in chemical balance, might underlie depression, and that antidepressant drugs induce plastic changes in neuronal connectivity, which gradually lead to improvements in neuronal information processing and recovery of mood

(Castren 2005). Drugs that selectively inhibit the reuptake of central monoamines have been used clinically to alleviate symptoms of depressive illnesses (Stahl 2000). Duloxetine binds selectively with high affinity to both norepinephrine (NE) and serotonin (5-HT) transporters and lacks affinity for monoamine receptors within the central nervous system. It has been suggested that dual inhibition of monoamine reuptake processes may offer advantages over other antidepressants currently in use. Consistent with other antidepressants, duloxetine, by acute administration, elevates extracellular monoamine levels, while by chronic administration it does not alter basal monoamine levels (Stahl 2000). Like the selective serotonin reuptake inhibitor fluoxetine, duloxetine inhibits neuronal cell firing; however in comparison with fluoxetine, duloxetine is a more potent serotonin reuptake inhibitor (Bymaster 2001).

Why it is important to do this review

Although pharmacological and psychological interventions are both effective for major depression, in primary and secondary care settings antidepressant (AD) drugs remain the mainstay of treatment (APA 2006; NICE 2010). Amongst ADs many different agents are available, including TCAs, monoamine oxidase inhibitors (MAOIs), SSRIs, serotonin-noradrenaline reuptake inhibitors (SNRIs, such as venlafaxine, duloxetine and milnacipran), and other newer agents (mirtazapine, reboxetine, bupropion). During the last 20 years, AD consumption has risen dramatically worldwide, mainly because of the increasing consumption of SSRIs and newer ADs, which have progressively become the most commonly prescribed ADs (Ciuna 2004). SSRIs are generally better tolerated than TCAs and there is evidence of similar efficacy (Anderson 2000). However, head-to-head comparison has provided contrasting findings. Amitriptyline, for example, may have the edge over SSRIs in terms of efficacy, and individual SSRIs and SNRIs may differ in terms of efficacy and tolerability (Hansen 2005; Cipriani 2006; Thase 2010; Watanabe 2011). Many reviews on duloxetine exist in current literature. Amongst these papers, Frampton and Plosker who reviewed the literature for short-term and long-term treatment with duloxetine in major depression (Frampton 2007), and Gartlehner and colleagues who reviewed 36 experimental and observational studies to assess comparative efficacy and safety of duloxetine for the treatment of acute-phase MDD in adults (Gartlehner 2009). These reviews are now quite outdated and neither has provided meta-analytic summaries. A group of researchers therefore agreed to join forces under the rubric of the Meta-Analyses of New Generation Antidepressants Study Group (MANGA Study Group), in order to systematically review all available evidence for each specific newer antidepressant. As of July 2012, we have completed an individual review for citalopram (Cipriani 2012), fluoxetine (Cipriani 2005), fluvoxamine (Omori 2010), mirtazapine (Watanabe 2011), milnacipran (Nakagawa 2009), escitalopram (Cipriani 2009c) and sertraline (Cipriani 2009b). The multiple-treatment meta-analysis of 12 new-generation antidepressants has also been published (Cipriani 2009a). In the present review, we report head-to-head comparisons not only between duloxetine and the other 11 new-generation antidepressants, but also between duloxetine and older antidepressants, providing detailed accounts of their comparative side effect profiles.

OBJECTIVES

1. To determine the efficacy of duloxetine in comparison with other anti-depressive agents in alleviating the acute symptoms of MDD.
2. To review acceptability of treatment with duloxetine in comparison with other anti-depressive agents.
3. To investigate the adverse effects of duloxetine in comparison with other anti-depressive agents.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials comparing duloxetine with all other active anti-depressive agents as monotherapy in the acute-phase treatment of major depression were included. Quasi-randomised trials, such as those allocating by using alternate days of the week, were excluded. For trials which have a cross-over design only results from the first randomisation period were considered.

Types of participants—The review included patients 18 years or older, of both sexes, with a primary diagnosis of major depression and studies adopting standardised criteria (DSM-III / DSM-III-R, DSM-IV (APA 2000), ICD-10 (WHO 1992), Feighner criteria (Feighner 1972) or Research Diagnostic Criteria (Spitzer 1972) to define patients suffering from unipolar major depression. Studies using ICD-9 were excluded, as it has only disease names and no diagnostic criteria. We included the following subtypes of major depression: chronic, with catatonic features, with melancholic features, with atypical features, with postpartum onset, and with seasonal pattern. We also included studies in which up to 20% of patients presented depressive episodes in bipolar affective disorder. A concurrent secondary diagnosis of another psychiatric disorder was not considered an exclusion criterion. A concurrent primary diagnosis of Axis I or II disorders was an exclusion criterion. AD trials in depressive patients with a serious concomitant medical illness were excluded.

Types of interventions—We examined duloxetine intervention in comparison with conventional treatment of acute major depression. We also examined duloxetine intervention in comparison with non-conventional (e.g., herbal products, such as *Hypericum*) anti-depressive agents (Linde 2008). We excluded trials in which duloxetine was compared with another type of psychopharmacological agent (i.e., anxiolytics, anticonvulsants or mood-stabilisers). We also excluded trials in which duloxetine was used as an augmentation strategy.

Eligible intervention

1. Duloxetine: any dose and pattern of administration.

Eligible comparators

2. Conventional anti-depressive agents: any dose and mode or pattern of administration:

- 2.1 Tricyclics (TCAs);
- 2.2 Heterocyclics;
- 2.3 SSRIs;
- 2.4 SNRIs;
- 2.5 MAOIs or newer ADs;
- 2.6 Other conventional psychotropic drugs.
- 3. Non-conventional anti-depressive agents:
 - 3.1 Herbal products;
 - 3.2 Other non-conventional anti-depressive agents.

Types of outcome measures

Primary outcomes

1. Response - acute phase: We examined cases regarding the number of patients (1) who responded to treatment by showing a reduction of at least 50% on the Hamilton Rating Scale for major depression (HRSD) (Hamilton 1960), Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery 1979), or any other depression scale, depending on the study authors' definition or (2) who were "much or very much improved" (score one or two) on the CGI-Improvement scale (Guy 1976) out of the total number of randomised patients. Where both are provided, we prefer the former criteria for judging response. The original authors' definitions of response and remission were not used in this review, to avoid possible outcome reporting bias (Furukawa 2007). We used response rate instead of a continuous symptom score for efficacy primary analysis to make the interpretation of results easier for clinicians (Guyatt 1998).

When studies report response rates at various time points throughout the trial, we determined *a priori* to subdivide the treatment indices - since one systematic review suggested that SSRIs begin to have observable beneficial effects in major depression during the first week of treatment - as follows (Taylor 2006):

- i. Response - early phase: between one and four weeks, with the time point closest to two weeks given preference.
- ii. Response - acute phase: between six and 12 weeks, with preference given to the time point given in the original study as the study endpoint.
- iii. Response - follow-up phase: between four and six months, with the time point closest to 24 weeks given preference.

The acute-phase treatment response rates were our primary outcome of interest.

Secondary outcomes

1. Response - early phase, and follow-up phase:

2. Remission - early phase, acute phase, and follow-up phase: We were interested in the number of patients who achieved remission, (1) showing ≤ 7 on HRSD-17, ≤ 8 for all the other longer versions of HRSD, and ≤ 11 on MADRS or (2) who were “not ill or borderline mentally ill” (score one or two) on the CGI-Severity score out of the total number of randomised patients. Where both were provided, we preferred the former criterion for judging remission.

3. Group mean scores at the end of the trial and change score on depression scale:

4. Social adjustment, social functioning, including the Global Assessment of Function (GAF) scores: (Hall 1995)

5. Health-related quality of life (QOL): We limited ourselves to SF-12 (Ware 1998); SF-36 (Ware 1992), HoNOS (Wing 1998) and the WHO 2009-QOL (WHOQOL Group 1998).

6. Costs to healthcare services:

7. Acceptability:

7.1 Total dropout: Number of patients who dropped out during the trial as a proportion of the total number of randomised patients.

7.2 Dropout due to inefficacy: Number of patients who dropped out during the trial because the duloxetine was ineffective as a proportion of the total number of randomised patients.

7.3 Dropout due to side effects: Number of patients who dropped out during the trial due to side effects, as a proportion of the total number of randomised patients.

7.4 Number of patients experiencing at least one side effect:

7.5 Number of patients experiencing the following specific side effects was sought:

- sleepiness/drowsiness
- insomnia
- dry mouth
- constipation
- problems urinating
- hypotension
- agitation/anxiety
- suicide wishes/gestures/attempts
- completed suicide
- vomiting/nausea
- diarrhoea

To avoid missing any relatively rare or unexpected side effects in the data extraction phase, we collected all side-effect data reported in the literature and discussed ways to summarise them post hoc. We extracted descriptive data regarding side-effect profiles from all available studies. Only studies reporting the number of patients experiencing individual side effects were retained. Due to a lack of consistent reporting of side effects, which came primarily from the study authors' descriptions, we combined terms describing similar side effects; for example, we combined "dry mouth", "reduced salivation" and "thirst" into "dry mouth". All side-effect categories were then grouped by organ system, such as neuropsychiatric, gastrointestinal, respiratory, sensory, genitourinary, dermatological and cardiovascular, in accordance with the advice of a previous study (Mottram 2006).

Search methods for identification of studies

Cochrane Depression, Anxiety and Neurosis (CCDAN) Group's Specialised Register (CCDANCTR)—The Cochrane Depression, Anxiety and Neurosis Group (CCDAN) maintain two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies based register. The CCDANCTR-References Register contains over 29,500 reports of randomised controlled trials in depression, anxiety and neurosis. Approximately 65% of these references have been tagged to individual, coded trials. The coded trials are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual. Please contact the CCDAN Trials Search Co-ordinator (TSC) for further details. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-), EMBASE (1974-) and PsycINFO (1967-); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organization's trials portal (ICTRP), ClinicalTrials.gov, drug companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Details of CCDAN's generic search strategies can be found on the Group's website.

Electronic searches—The CCDANCTR-Studies Register was searched by the TSC using the following search strategy:

Diagnosis = Depress* or Dysthymi* or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Disorder" or "Affective Symptoms"

and

Intervention = Duloxetine

The CCDANCTR-References was searched using similar terms to identify additional untagged/uncoded references:

Keyword = Depress* or Dysthymi* or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Disorder" or "Affective Symptoms"

and

Free-Text = Duloxetine

Searches were conducted to March 2012. No language restrictions were applied.

Other trial registers: CCDAN's TSC also searched Clinicalstudyresults.org to December 2011 (before this website was phased out) together with ClinicalTrials.gov and the WHO Trials Portal (ICTRP) to July 2012, for additional published, unpublished or ongoing studies.

We searched trial databases of the following drug-approving agencies: the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, the European Medicines Agency (EMA) in the EU, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the Therapeutic Goods Administration (TGA) in Australia. We also searched ongoing trial registers such as clinicaltrials.gov in the USA, International Standard Randomised Controlled Trial Number Register (ISRCTN) and the National Research Register in the UK, Nederland's Trial Register in the Netherlands, European Union Drug Regulating Authorities Clinical Trials (EudraCT) in the EU, UMIN-CTR in Japan, the Australian Clinical Trials Registry in Australia and the clinical trial register of Eli Lilly (duloxetine manufacturer): <http://www.lillytrials.com/results/results.html>. These searches were undertaken in November 2010.

Searching other resources

1. Handsearches: Appropriate journals and conference proceedings relating to duloxetine treatment for major depression have already been hand-searched and incorporated into the CCDANCTR databases.

2. Personal communication: Pharmaceutical companies and experts in this field were asked if they knew of any study that met the inclusion criteria of this review.

3. Reference checking: Reference lists of the included studies, previous systematic reviews and major textbooks of affective disorder written in English were checked for published reports and citations of unpublished research.

Data collection and analysis

Selection of studies—Two review authors independently checked to ensure that studies relating to duloxetine generated by the search strategies of the CCDANCTR-References and the other complementary searches met the inclusion criteria, firstly based on the title and abstracts. All of the studies that were rated as possible candidates by either of the two review authors were added to the preliminary list, and their full texts were retrieved. AC, MN, MP, MK and CT then assessed all of the full text articles in this preliminary list to see if they still met the inclusion criteria. If the raters disagreed, the final rating was made by consensus with the involvement - if necessary - of another member of the review group (CB or TAF). Considerable care was taken to exclude duplicate publications.

Data extraction and management—AC, MK and MP extracted data from the included studies. Again, any disagreement was discussed, and decisions were documented. If necessary, we contacted authors of studies for clarification. We extracted the following data:

- i. participant characteristics (age, sex, depression diagnosis, comorbidity, depression severity, antidepressant treatment history for the index episode, study setting);
- ii. intervention details (intended dosage range, mean daily dosage actually prescribed, co-intervention if any, duloxetine as investigational drug or as comparator drug, sponsorship);
- iii. outcome measures of interest from the included studies.

The results were compared with those in the completed reviews of individual antidepressants in *The Cochrane Library*. If the trial was a three (or more)-armed trial involving a placebo arm, the data were extracted from the placebo arm as well.

Assessment of risk of bias in included studies—Two review authors independently assessed trial quality in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This set of criteria is based on evidence of associations between effect overestimation and a high risk of bias in an article, such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting. The categories are defined below.

- Low risk of bias
- High risk of bias
- Unclear risk of bias

If the raters disagreed, the final rating was made by consensus with the involvement (if necessary) of another member of the review group. Non-congruence in quality assessment was reported as percentage disagreement. The ratings were also compared with those in the completed reviews of individual antidepressants in *The Cochrane Library*. If there were any discrepancies, they were fed back to the authors of the completed reviews.

Measures of treatment effect—All comparisons were performed between duloxetine and comparator ADs as a class and as individual ADs.

1. Dichotomous data: For dichotomous, or event-like, data, odds ratios (ORs) were calculated with their 95% confidence intervals (CIs). For statistically significant results, we calculated the number needed to treat to provide benefit (NNTB) and the number needed to treat to induce harm (NNTH) as the inverse of the risk difference.

2. Continuous data: For continuous data, mean differences (MD) or standardised mean differences (SMD) were calculated with their 95% CIs. MDs were used where the same scale was used to measure an outcome; SMDs were employed where different scales were used to measure the same outcome.

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, despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in major depression, we only used data from the first phase of the cross-over studies. No crossover studies were identified for this version of the review. However, we are aware that cross-over trials for which only first-period data are available should be considered to be at risk of bias (Higgins 2011), so careful attention will be paid to retrieve only unbiased data available from such studies in the next updates of the review.

2. Cluster-randomised trials: We did not identify any cluster-randomised trials for this version of the review. Should they be identified in a future update, we plan to use the generic inverse variance technique, if such trials have been appropriately analysed taking into account intraclass correlation coefficients to adjust for cluster effects.

Dealing with missing data

1. Dichotomous data: Responders and remitters to treatment were calculated on the strict intention-to-treat (ITT) basis: dropouts were included in this analysis. Where participants were excluded from the trial before the endpoint, we assumed that they experienced a negative outcome by the end of the trial (e.g., failure to respond to treatment). We examined the validity of this decision in sensitivity analyses by applying worst- and best-case scenarios (that is, only missing data were assumed either as responder or non-responder in the corresponding sensitivity analysis).

When dichotomous outcomes were not reported but baseline mean, endpoint mean and those standard deviations (SDs) of the HRSD (or other depression scale) were provided, we converted continuous outcome data expressed as mean and SD into the number of responding and remitted patients, according to the validated imputation method (Furukawa 2005). We examined the validity of this imputation in the sensitivity analyses. Where SDs were not reported, we contacted trial authors and asked them to supply the data. When only the standard error (SE) or t-statistics or P values were reported, SDs were calculated according to Altman (Altman 1996). In the absence of data from the authors, we substituted SDs by those reported in other studies in the review (Furukawa 2006).

2. Continuous data: When there were missing data and the method of “last observation carried forward” (LOCF) had been used to perform an ITT analysis, then the LOCF data were used. When SDs were missing, we borrowed SDs from other similar trials, if possible, or presented data descriptively.

Assessment of heterogeneity—Skewed data and non-quantitative data were presented descriptively. An outcome whose minimum score is zero could be considered skewed when the mean was smaller than twice the SD. Heterogeneity between studies was investigated by

the I^2 statistic (Higgins 2003) (and I^2 equal to or more than 50% was considered indicative of heterogeneity) and by visual inspection of the forest plots. Considering that the value of the I^2 depends on the sample size of the included studies, magnitude and direction of effects and the strength of evidence for heterogeneity, we used this arbitrary threshold for a preliminary evaluation. If the I^2 value fell below 50% but the direction and magnitude of treatment effects were suggestive of important heterogeneity, we investigated the potential sources of heterogeneity. Finally, we performed subgroup analyses to investigate heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases—Data from included studies were entered into a funnel plot (trial effect against trial variance) to investigate small-study effects (Sterne 2000). We used the tests for funnel plot asymmetry only when there were at least 10 studies included in the meta-analysis, and results were interpreted cautiously, with visual inspection of the funnel plots (Higgins 2011). When evidence of small-study effects was identified, we investigated possible reasons for funnel plot asymmetry, including publication bias.

Data synthesis—The primary analysis used the odds ratio (OR) with a random-effects model, because it has the highest generalisability in empirical examination of summary effect measures for meta-analyses (Furukawa 2002a). The robustness of this summary measure was routinely examined by checking the fixed-effect model OR and the random-effects model risk ratios (RRs). Material differences between the models were reported. A P value of less than 0.05 and a 95% CI were considered statistically significant.

Fixed-effect analyses were performed routinely for the continuous outcomes as well, to investigate the effect of the choice of method on the estimates. Material differences between the models were reported. Skewed data and non-quantitative data were presented descriptively. An outcome was considered skewed when the mean was smaller than twice the SD. In terms of change score, data were difficult to depict as skewed or not as the possibility existed for negative values; therefore, we entered all of the results of this outcome into a meta-analysis.

Subgroup analysis and investigation of heterogeneity—Where possible, we performed the following subgroup analyses for the primary outcome, for the following *a priori* reasons. Results were interpreted with caution, since multiple comparisons could lead to false positive conclusions (Oxman 1992).

1. Duloxetine dosing (fixed low dosage, fixed standard dosage, fixed high dosage; flexible low dosage, flexible standard dosage, flexible high dosage): Existing evidence implies that low dosage antidepressants may be associated with better outcomes - both in terms of efficacy and side effects - than standard or high dosage antidepressants (Bollini 1999; Furukawa 2002b). In addition, a fixed versus flexible dosing schedule may affect estimates of treatment effectiveness (Khan 2003). In the case of duloxetine, based on the Defined Daily Dosage (DDD) by WHO (WHO 2009a), low dosage is referred to as < 60, standard dosage to ≥ 60 but < 90, and high dosage to ≥ 90 mg/day. We categorised studies by intended maximum dosage of duloxetine.

2. Comparator dosing (low dosage, standard dosage, and high dosage): It is easy to imagine that people taking a comparator drug are less likely to complete a study if they are taking a high dosage of the comparator drug. We categorised studies by the intended maximum dose of the comparator based on the DDD.

3. Depression severity (severe major depression, moderate/mild major depression): “Severe major depression” was defined by a threshold baseline severity score for entry of 25 or more for HRSD and 31 or more for MADRS (Dozois 2004; Müller 2003).

4. Treatment settings (psychiatric inpatients, psychiatric outpatients, primary care): Because depressive disorder in primary care has a different profile than that of psychiatric inpatients or outpatients (Suh 1997), it is possible that results obtained from either of these settings may not be applicable to the other settings (Depression Guideline Panel 1993).

5. Elderly patients (≥ 65 years of age), separately from other adult patients: Older people may be more vulnerable to side effects associated with antidepressants and decreased dosage is often recommended for them (Depression Guideline Panel 1993).

If the CIs of ORs in the groups did not overlap, potential sources of heterogeneity were investigated.

Because the number of *a priori* planned subgroup analyses now appears excessive in comparison with the identified studies, we will consider reducing the number of subgroup analyses or adjusting the level of significance to account for making multiple comparisons in the next update.

Sensitivity analysis—The following sensitivity analyses for primary outcome were planned *a priori*. By limiting the included studies to those with higher quality (analyses one to five) or to those free from some “bias” (analyses six to nine), we examined whether the results changed and we intended to check for the robustness of the observed findings.

1. We excluded trials with unclear concealment of random allocation, unclear double blinding, or both.
2. We excluded trials with a dropout rate greater than 20%.
3. We performed the worst-case scenario ITT: that all patients in the experimental group experienced the negative outcome and all those in the comparison group experienced the positive outcome.
4. We performed the best-case scenario ITT: that all patients in the experimental group experienced the positive outcome and all those in the comparison group experienced the negative outcome.
5. We excluded trials for which the response rates had to be calculated based on the imputation method (Furukawa 2005) and for which the SD had to be ‘borrowed’ from other trials (Furukawa 2006).

6. We examined a “wish bias” by comparing the trials where duloxetine was used as an investigational drug, the drug that was used as a new compound, to the trials where duloxetine was used as a comparator, since some evidence suggests that a new antidepressant might perform worse when used as a comparator than when used as an investigational agent (Barbui 2004).
7. We excluded trials funded by, or with at least one author affiliated with, a pharmaceutical company marketing duloxetine. This sensitivity analysis is particularly important in light of the recent repeated findings that funding strongly affects outcomes of research studies (Als-Nielsen 2003; Lexchin 2003; Montgomery 2004; Procyshyn 2004; Bhandari 2004; Perlis 2005) and because industry sponsorship and authorship of clinical trials has increased over the past 20 years (Buchkowsky 2004).
8. We excluded studies that included patients with bipolar depression.
9. We excluded trials that included patients with psychotic features.

Our routine application of random-effects and fixed-effect models, as well as our secondary outcomes of remission rates and continuous severity measures, may be considered additional forms of sensitivity analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search—Initially, we identified 99 references. After reading the abstracts, 41 references were considered relevant for our review and retrieved for more detailed evaluation. Among them, we found four studies comparing duloxetine with two new antidepressant drugs: Lu AA21004 (three studies) and AZD2066 (one study). Unfortunately, the majority of information about these drugs is still not published and we did not manage to retrieve unpublished material. We decided to consider these trials as awaiting assessment studies, because the inclusion and analysis of only a limited subgroup of published studies might significantly increase the risk of giving biased results. We will include this information in the next update of the present review.

Included studies—A total of 16 studies were included in this systematic review. Of these, three trials were unpublished (ID#3327 (HMAQ B); ID#4091 (HMAQ A); ID#7999 (HMCQ)). Attempts to contact the authors for additional unpublished information were successful in eight cases (with additional data provided by authors or pharmaceutical industry) and unsuccessful in five (Wade 2007; Cutler 2009; Higuchi 2009a; Tourian 2009; Patel 2011).

Sample Size: The mean sample size per arm was 129 participants (range 33 to 274). Only two studies recruited fewer than 200 participants overall (Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)).

Study design: All included studies were reported to be double-blind, apart from one Indian study which was designed as open-label study (Patel 2011). Five studies were two-armed (Khan 2007 (SCT-MD-23); Lee 2007 (HMCV); Wade 2007; Perahia 2008 (HMBU); Patel 2011) and the remaining 11 were multi-armed and all of them were placebo-controlled trials.

Country: All RCTs were multi-centre studies and the majority of them (10 out of 16 RCTs, (62.5%)) had been carried out in Europe, US or Canada: one study in Europe only (Perahia 2006 (HMAQ B)), one study in Europe and Canada (Wade 2007), one study in US or Canada (Perahia 2008 (HMBU)) and seven studies in the US only (Goldstein 2004 (HMAQ B); ID#3327 (HMAQ B); ID#4091 (HMAQ A); Khan 2007 (SCT-MD-23); Nierenberg 2007 (HMCV); Cutler 2009; Tourian 2009). One study randomised patients in Japan (Higuchi 2009a), one in India (Patel 2011) and one in China, Taiwan, Korea and Brazil (Lee 2007 (HMCV)). For the three remaining studies, the country of origin was unclear or not specified (Goldstein 2002 (HMAQ A); Detke 2004 (HMAQ A); ID#7999 (HMCQ)).

Age: Ten studies randomised patients aged 18 years or more (Detke 2004 (HMAQ A); Goldstein 2004 (HMAQ B); ID#4091 (HMAQ A); ID#7999 (HMCQ); Khan 2007 (SCT-MD-23); Perahia 2006 (HMAQ B); Lee 2007 (HMCV); Nierenberg 2007 (HMCV); Perahia 2008 (HMBU); Tourian 2009) and six studies only patients aged between 18 and 65 years (Goldstein 2002 (HMAQ A); Wade 2007; Cutler 2009; Higuchi 2009a; ID#3327 (HMAQ B); Patel 2011).

Diagnosis: All studies included patients with major depressive disorder (MDD) only, but in one study it was unclear whether a few patients with bipolar depression were included (Higuchi 2009a). As per protocol, RCTs were included in the present review only if patients with bipolar disorder were less than 20% in each study.

Setting/participants: Thirteen trials enrolled only out-patients, two recruited both in and out-patients (Lee 2007 (HMCV); Higuchi 2009a) and in one study, information about the setting was not reported (Patel 2011). All patients had a formal diagnosis of major depression (or MDD) according to DSM IV (or DSM IV-TR) criteria or ICD 10 criteria.

Interventions and comparators: We found 11 studies (overall 3304 participants) comparing duloxetine with one SSRI (six studies versus paroxetine, three studies versus escitalopram and two versus fluoxetine), four studies (overall 1978 participants) comparing duloxetine with a newer ADs (three with venlafaxine and one with desvenlafaxine, respectively) and one study (overall 453 participants) comparing duloxetine with an antipsychotic drug which is also used as an antidepressive agent, quetiapine (Cutler 2009). Even though in the review protocol we reported that studies comparing duloxetine with antipsychotics would be excluded, recently evidence has been published about the use of atypical antipsychotics in patients with unipolar major depression (Maher 2011). After an authors' panel discussion, we decided to include such studies in the present review to shed

light on head-to-head comparative effectiveness of all active drugs used in clinical practice for unipolar major depression. We found four three-arm trials: two studies comparing duloxetine (40 to 120 mg/day) with fluoxetine (20 mg/day) or placebo (ID#3327 (HMAQ B); Goldstein 2002 (HMAQ A)); one study comparing duloxetine with venlafaxine 75 mg/day or venlafaxine 150 mg/day (ID#7999 (HMCQ)); and one study comparing duloxetine (60-120 mg/day) with escitalopram (10-20 mg/day) or placebo (Nierenberg 2007 (HMCQ)). There were seven four-arm trials: two RCTs compared duloxetine 120 mg/day with duloxetine 80 mg/day, paroxetine 20 mg/day and placebo (Detke 2004 (HMAQ A); Perahia 2006 (HMAQ B)), two studies compared duloxetine 40 mg/day with duloxetine 80 mg/day, paroxetine 20 mg/day and placebo (Goldstein 2004 (HMAQ B); ID#4091 (HMAQ A)); one trial compared desvenlafaxine 50 mg/day with desvenlafaxine 100 mg/day, duloxetine 60 mg/day and placebo (Tourian 2009), one RCT compared quetiapine XR 150 mg/day with quetiapine XR 300 mg/day, duloxetine 60 mg/day and placebo (Cutler 2009) and one study compared duloxetine 40 mg/day with duloxetine 60 mg/day, paroxetine 20-40 mg/day and placebo (Higuchi 2009a).

Outcomes: Of the included 16 studies, all reported efficacy data (either as dichotomous or as continuous outcome) and tolerability/acceptability data that could be entered into a meta-analysis. All studies used HDRS or CGI as rating scale of choice for primary or secondary outcome measures and the great majority of the identified studies used MADRS, as well (13 out of 16 RCTs). All studies reported dropouts due to any reason and among them 15 reported dropouts due to side effects and 12 dropouts due to inefficacy. Only two studies did not report the number of patients experiencing individual side effects (Cutler 2009; Patel 2011).

Excluded studies—Of the 41 references retrieved for more detailed evaluation, 15 articles did not meet our inclusion criteria and were excluded because of one of the following reasons: wrong/non-randomised design (four articles), review/pooled analysis (three articles), wrong comparison (two articles), wrong intervention (four articles), duplicate publications or subgroup analysis (one article) and wrong diagnosis/population (one article).

Ongoing studies—Four ongoing studies were identified (2008-004642-92; NCT01140906; NCT01153009; NCT01288079).

Studies awaiting classification—Five studies were classified as awaiting assessment (Joubert 1997; NCT00635219; NCT00672620; NCT00811252; NCT01145755).

Risk of bias in included studies

See: Included studies, Figure 1, Figure 2.

Our judgment about the overall risk of bias in the individual studies is illustrated in Figure 1 and Figure 2. The methodological quality of these included studies was overall not good. This type of reporting has been associated with an overestimate of the estimate of effect (Schulz 1995) and this should be considered when interpreting the results.

Allocation—The majority of studies reported the methods of generating random sequence, in which “a computer originated schedule” was used, however, only one study reported enough details on allocation concealment (Wade 2007). We were not assured that bias was minimised during the allocation procedure in the other studies, yet the great majority of them reported that the participants allocated to each treatment group were “similar”, “the same”, “not significantly different”, “comparable” or “matched”.

Blinding—All RCTs (100%) described their design as “double blind”, however, no tests were conducted to ensure successful blinding and only one study reported full details about blinding (Wade 2007).

Incomplete outcome data—Total dropout rate was overall relatively high, ranging from 9% (Detke 2004 (HMA Y A)) to 42% (Detke 2004 (HMA Y A); Goldstein 2004 (HMA T B); ID#7999 (HMCQ); Perahia 2006 (HMA Y B)). There were 11 studies (69%) where the total dropout rates were higher than 20%.

Selective reporting—The study protocol was not available for the majority studies and some of them did not report mean changes with SDs of continuous primary efficacy variables (Cutler 2009; Tourian 2009).

Other potential sources of bias—All the included studies were funded by industry and only four studies were not sponsored by the manufacturer of duloxetine (they were sponsored by the comparative treatments’ manufacturers: escitalopram (Khan 2007 (SCT-MD-23); Wade 2007), desvenlafaxine (Tourian 2009) and quetiapine (Cutler 2009), respectively).

Effects of interventions

The included studies did not report on all the outcomes that were pre-specified in the protocol of this review. Outcomes of clear relevance to patients and clinicians, in particular, patient’s and their relatives’ attitudes to treatment, their ability to return to work and resume normal social functioning, health-related quality of life measures and costs to healthcare services were reported in some of the included studies with not enough details for re-analysis (Wade 2007; Perahia 2008 (HMBU); ID#7999 (HMCQ); ID#3327 (HMAQ B)) or in the majority of trials not reported at all. Overall, 5265 patients were available for assessing efficacy (2814 participants randomised to duloxetine and 2451 to another active treatment) and 5735 for examining acceptability of treatments (3001 participants allocated to duloxetine and 2734 to another active treatment). Evidence of differences was found and details are listed below. Even though it was planned and allowed in the review protocol, it was not necessary to use imputation methods for analysing data, neither for dichotomous nor for continuous outcomes.

The results of the present systematic review were reported comparison by comparison (grouping them into three different drug classes: older ADs, SSRIs and newer ADs) and by outcome, following the review protocol. The forest plots were organised according to the relevance of outcomes, as reported in the review protocol. For adverse events, all the retrieved information about the adverse events specified in the review protocol were

reported (either statistically or non-statistically significant). Remaining adverse events were only reported when statistically significant (non-statistically significant results about adverse events are presented in Table 1).

1. DULOXETINE versus older ADs—No studies were found comparing duloxetine with older antidepressants.

2. DULOXETINE versus SSRIs

PRIMARY OUTCOME

EFFICACY - Number of patients who responded to treatment (6 to 12 weeks): There was no evidence that duloxetine was less or more effective than any SSRI (odds ratio (OR) 1.31, 95% confidence interval (CI) 0.87 to 1.97, $P = 0.19$; three trials, 1120 participants, when duloxetine was compared with escitalopram; OR 0.81, 95% CI 0.46 to 1.44, $P = 0.47$; two trials, 222 participants, when duloxetine was compared with fluoxetine; OR 1.12, 95% CI 0.88 to 1.43, $P = 0.36$; six trials, 1821 participants, when duloxetine was compared with paroxetine - Analysis 1.1; Figure 3).

SECONDARY OUTCOMES

1) EFFICACY - Number of patients who responded to treatment

a) Early response (1 to 4 weeks): No data available.

b) Follow-up response (16 to 24 weeks): There was no evidence that duloxetine was less effective than escitalopram (OR 1.32, 95% CI 0.79 to 2.22, $P = 0.29$; one trial, 295 participants - Analysis 2.1) - we found no data regarding other SSRIs.

2) EFFICACY - Number of patients who remitted

a) Acute-phase treatment (6 to 12 weeks): There was no evidence that duloxetine was less or more effective than SSRIs (Analysis 3.1).

b) Early remission (1 to 4 weeks): No data available.

c) Follow-up remission (16 to 24 weeks): There was no evidence that duloxetine was less effective than escitalopram (Analysis 4.1) - we found no data regarding other SSRIs.

3) EFFICACY - Mean change from baseline

a) Acute-phase treatment: between 6 and 12 weeks: No evidence was found that duloxetine was less or more effective than SSRIs (Analysis 5.1).

b) Early response (1 to 4 weeks): There was no evidence that duloxetine was more effective than paroxetine (mean difference (MD) -0.51 , 95% CI -1.41 to 0.40 , $P = 0.27$; two trials, 353 participants - Analysis 6.1) - we found no data regarding other SSRIs.

c) Follow-up response (16 to 24 weeks): There was no evidence that duloxetine was less effective than escitalopram (MD 1.34 , 95% CI -0.21 to 2.89 , $P = 0.09$; one trial, 287 participants - Analysis 7.1) - we found no data regarding other SSRIs.

4) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to healthcare services: No data available.

5) ACCEPTABILITY - Dropout rate: a) There was evidence that duloxetine was associated with a higher overall rate of discontinuations than escitalopram (OR 1.62, 95% CI 1.01 to 2.62; $P = 0.05$; three trials, 1120 participants) (Analysis 8.1; Figure 4); by contrast, no difference was found between duloxetine and fluoxetine or paroxetine in terms of number of patients withdrawing due to any cause (Analysis 8.1; Figure 4).

b) No differences were found in terms of discontinuation due to inefficacy (Analysis 9.1).

c) There was evidence that duloxetine was associated with a higher rate of discontinuations due to side effects than escitalopram (OR 2.31, 95% CI 1.15 to 4.65; $P = 0.05$; three trials, 1120 participants) (Analysis 10.1). By contrast, no difference was found between duloxetine and fluoxetine or paroxetine in terms of number of patients withdrawing due to side effects (Analysis 10.1)

6) TOLERABILITY

Total number of patients experiencing at least some side effects: There was weak evidence that duloxetine was associated with a higher rate of adverse events than paroxetine (OR 1.24, 95% CI 0.99 to 1.55; $P = 0.06$; six trials, 1870 participants) (Analysis 11.1). By contrast, there was no evidence that duloxetine was associated with a higher rate of participants experiencing adverse events than other SSRIs (namely, escitalopram or fluoxetine).

a) Anxiety/agitation: There was no evidence that duloxetine was associated with a lower or higher rate of participants experiencing anxiety/agitation than SSRIs (Analysis 16.1).

b) Constipation: There was no evidence that duloxetine was associated with a higher rate of participants experiencing diarrhoea than SSRIs (Analysis 21.1).

c) Diarrhoea: There was no evidence that duloxetine was associated with a lower rate of participants experiencing diarrhoea than SSRIs (Analysis 23.1).

d) Dry mouth: There was evidence that duloxetine was associated with a higher rate of participants experiencing dry mouth than escitalopram (OR 1.84, 95% CI 1.29 to 2.63; $P = 0.0008$; three trials, 1120 participants) (Analysis 26.1). By contrast, there was no evidence that duloxetine was associated with a higher rate of participants experiencing adverse events than other SSRIs (namely, fluoxetine or paroxetine) (Analysis 26.1).

e) Hypotension: No data reported.

f) Insomnia: There was no evidence that duloxetine was associated with a higher rate of participants experiencing insomnia than SSRIs (Analysis 39.1).

g) Nausea/vomiting: There was evidence that duloxetine was associated with a higher rate of participants experiencing nausea/vomiting than escitalopram (OR 1.82, 95% CI 1.36 to

2.44; $P < 0.0001$; three trials, 1120 participants) and paroxetine (OR 1.46, 95% CI 1.13 to 1.89; $P = 0.004$; five trials, 1573 participants) (Analysis 41.1). By contrast, there was no evidence that duloxetine was associated with a higher rate of participants experiencing adverse events than fluoxetine (Analysis 41.1).

h) Sedation/drowsiness: No data reported.

i) Sleepiness/somnolence: There was no evidence that duloxetine was associated with a lower or higher rate of participants experiencing sleepiness/somnolence than SSRIs (Analysis 57.1).

j) Urination problems: There was no evidence that duloxetine was associated with a lower or higher rate of participants experiencing urination problems than SSRIs (Analysis 67.1).

k) Suicide wishes/gestures/attempts: No data reported.

l) Deaths (all cause)/completed suicide: No data reported.

m) Other adverse events: Duloxetine was associated with a lower rate of participants experiencing abdominal pain than fluoxetine (OR 0.27, 95% CI 0.08 to 0.88, $P = 0.03$; two trials, 222 participants - Analysis 43.1). No statistically significant results were found for escitalopram and paroxetine.

3. DULOXETINE versus newer ADs

PRIMARY OUTCOME

EFFICACY - Number of patients who responded to treatment (6 to 12 weeks): The analysis of primary outcome found that duloxetine was not statistically less effective than venlafaxine (OR 1.18, 95% CI 0.82 to 1.68, $P = 0.51$, one trial, 332 participants) or desvenlafaxine (OR 0.82, 95% CI 0.56 to 1.20, $P = 0.30$, one trial, 474 participants) (Analysis 1.2).

SECONDARY OUTCOMES

1) EFFICACY - Number of patients who responded to treatment

b) Early response (1 to 4 weeks): No data available.

c) Follow-up response (16 to 24 weeks): There was no evidence that duloxetine was less effective than venlafaxine (OR 1.06, 95% CI 0.73 to 1.55, $P = 0.75$; one trial, 491 participants - Analysis 2.2). No data available for the other comparisons with desvenlafaxine.

2) EFFICACY - Number of patients who remitted

a) Acute-phase treatment (6 to 12 weeks): There was no evidence that duloxetine was less effective than venlafaxine (OR 1.13, 95% CI 0.83 to 1.53, $P = 0.44$; two trials, 823 participants - Analysis 3.2). No differences in terms of remission were also found between duloxetine and desvenlafaxine (Analysis 3.2).

b) Early remission (1 to 4 weeks): No data available.

c) Follow-up remission (16 to 24 weeks): No data available.

3) EFFICACY - Mean change from baseline

a) Acute-phase treatment: between 6 and 12 weeks: There was no evidence that duloxetine was less effective than venlafaxine (MD 0.60, 95% CI -0.46 to 1.65, $P = 0.27$; two trials, 648 participants - Analysis 5.2). No data available for the other comparison with desvenlafaxine.

b) Early response (1 to 4 weeks): There was no evidence that duloxetine was less effective than venlafaxine (MD -0.13, 95% CI -0.94 to 1.067, $P = 0.74$; two trials, 608 participants - Analysis 6.2). No data available for the other comparison with desvenlafaxine.

c) Follow-up response (16 to 24 weeks): No data available.

4) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to healthcare services: No data available.

5) ACCEPTABILITY - Dropout rate: a) There was evidence that duloxetine was associated with a higher overall rate of discontinuations than venlafaxine (OR 1.56, 95% CI 1.14 to 2.15; $P = 0.01$; three trials, 1051 participants - Analysis 8.2; Figure 5). No differences were found between duloxetine and desvenlafaxine (Analysis 8.2).

b) No differences were found in terms of discontinuation due to inefficacy between duloxetine and venlafaxine (Analysis 9.2). No data available for the other comparison with desvenlafaxine.

c) There was evidence that duloxetine was associated with a higher rate of discontinuations due to side effects than venlafaxine (OR 1.93, 95% CI 1.23 to 3.01; $P = 0.006$; three trials, 1051 participants) and than desvenlafaxine (OR 2.14, 95% CI 1.11 to 4.15; $P = 0.02$; one trial, 455 participants) (Analysis 10.2).

6) TOLERABILITY

Total number of patients experiencing at least one side effect: No difference was found between duloxetine and venlafaxine or desvenlafaxine in terms of total number of patients experiencing at least one side effect (Analysis 11.2).

a) Anxiety/agitation: There was no evidence that duloxetine was associated with a higher rate of participants experiencing anxiety/agitation than venlafaxine (Analysis 16.2). No data available for the other comparison with desvenlafaxine.

b) Constipation: There was no evidence that duloxetine was associated with a lower or higher rate of participants experiencing constipation than venlafaxine or desvenlafaxine (Analysis 21.2).

c) Diarrhoea: There was no evidence that duloxetine was associated with a higher rate of participants experiencing diarrhoea than venlafaxine (Analysis 23.2).

d) Dry mouth: There was no evidence that duloxetine was associated with a lower rate of participants experiencing dry mouth than venlafaxine (Analysis 26.2).

e) Hypotension: No data available.

f) Insomnia: There was no evidence that duloxetine was associated with a lower rate of participants experiencing insomnia than venlafaxine or desvenlafaxine (Analysis 39.2).

g) Nausea/vomiting: There was evidence that duloxetine was associated with a higher rate of participants experiencing nausea/vomiting than desvenlafaxine (OR 1.53, 95% CI 1.00 to 2.37, $P = 0.05$; one trial, 455 participants - Analysis 41.2). There was no evidence that duloxetine was associated with a higher rate of participants experiencing nausea/vomiting than venlafaxine (Analysis 39.2).

h) Sedation/drowsiness: No data reported.

i) Sleepiness/somnolence: There was no evidence that duloxetine was associated with a higherrate of participants experiencing sleepiness/somnolence than venlafaxine or desvenlafaxine (Analysis 57.2).

j) Urination problems: No data reported.

k) Suicide wishes/gestures/attempts: No data available.

l) Deaths (all cause)/completed suicide: No data available.

l) Other adverse events: Duloxetine was associated with a higher rate of participants experiencing dizziness (OR 1.68, 95% CI 1.11 to 2.55, $P = 0.01$; two trials, 823 participants - Analysis 24.2) and yawning (OR 4.22, 95% CI 1.75 to 10.17, $P = 0.001$; one trial, 491 participants - Analysis 74.2) than venlafaxine. Duloxetine was associated with a higher rate of participants experiencing decreased appetite than desvenlafaxine (OR 2.18, 95% CI 1.25 to 3.83, $P = 0.006$; one trial, 455 participants - Analysis 17.2).

4. DULOXETINE versus antipsychotics (quetiapine)

PRIMARY OUTCOME

EFFICACY - Number of patients who responded to treatment (6 to 12 weeks): The analysis of primary outcome found that duloxetine was not statistically less effective than quetiapine (OR 1.27, 95% CI 0.86 to 1.88, $P = 0.23$; one trial, 453 participants) (Analysis 1.2).

SECONDARY OUTCOMES

1) EFFICACY - Number of patients who responded to treatment

b) Early response (1 to 4 weeks): No data available.

c) Follow-up response (16 to 24 weeks): No data available.

2) EFFICACY - Number of patients who remitted

a) Acute-phase treatment (6 to 12 weeks): No differences in terms of remission were also found between duloxetine and quetiapine (Analysis 3.2).

b) Early remission (1 to 4 weeks): No data available.

c) Follow-up remission (16 to 24 weeks): No data available.

3) EFFICACY - Mean change from baseline

a) Acute-phase treatment: between 6 and 12 weeks: No data available for the comparison between duloxetine and quetiapine.

b) Early response (1 to 4 weeks): No data available for the comparison between duloxetine and quetiapine.

c) Follow-up response (16 to 24 weeks): No data available.

4) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to healthcare services: No data available.

5) ACCEPTABILITY - Dropout rate: a) No differences were found between duloxetine and quetiapine (Analysis 8.2).

b) No data available for the comparison between duloxetine and quetiapine.

c) No data available for the comparison between duloxetine and quetiapine.

6) TOLERABILITY Total number of patients experiencing at least one side effect: No data available for the comparison with quetiapine.

a) Anxiety/agitation: No data available for the comparison between duloxetine and quetiapine.

b) Constipation: There was no evidence that duloxetine was associated with a lower or higher rate of participants experiencing constipation than quetiapine (Analysis 21.2).

c) Diarrhoea: There was evidence that duloxetine was associated with a higher rate of participants experiencing diarrhoea than quetiapine (OR 3.20, 95% CI 1.45 to 7.09, $P = 0.004$; one trial, 453 participants - Analysis 23.2).

d) Dry mouth: There was evidence that duloxetine was associated with a lower rate of participants experiencing dry mouth than quetiapine (OR 0.41, 95% CI 0.26 to 0.66, $P = 0.0003$; one trial, 453 participants - Analysis 26.2).

e) Hypotension: No data available.

f) *Insomnia*: There was evidence that duloxetine was associated with a higher rate of participants experiencing insomnia than quetiapine (OR 12.99, 95% CI 4.39 to 38.46, $P < 0.00001$; one trial, 453 participants - Analysis 39.2).

g) *Nausea/vomiting*: There was evidence that duloxetine was associated with a higher rate of participants experiencing nausea/vomiting than quetiapine (OR 6.63, 95% CI 3.89 to 11.31, $P < 0.00001$; one trial, 453 participants - Analysis 41.2).

h) *Sedation/drowsiness*: No data reported.

i) *Sleepiness/somnolence*: There was evidence that duloxetine was associated with a lower rate of participants experiencing sleepiness/somnolence than quetiapine (OR 0.42, 95% CI 0.25 to 0.73, $P = 0.002$; one trial, 453 participants - Analysis 57.2).

j) *Urination problems*: No data reported.

k) *Suicide wishes/gestures/attempts*: No data available.

l) *Deaths (all cause)/completed suicide*: There was one death in the quetiapine XR 150 mg/day arm of the study carried out by Cutler and colleagues (Cutler 2009), however no further details were provided in the published report.

m) *Other adverse events*: Duloxetine was associated with a higher rate of participants experiencing headache than quetiapine (OR 1.95, 95% CI 1.12 to 3.41, $P = 0.02$; one trial, 453 participants - Analysis 32.2).

SUBGROUP ANALYSES

1) *Duloxetine dosing*: There were only three studies using duloxetine at 40 mg/day (fixed-dose regimen): Goldstein 2004 (HMA T B); Higuchi 2009a; ID#4091 (HMA T A). Three other studies used a flexible dose regimen, starting from 40 mg/day (Goldstein 2002 (HMA Q A); ID#3327 (HMA Q B) and Patel 2011), however, the great majority of patients received higher doses of duloxetine just after one or two weeks. In the first two HMA Q studies (identical protocols) duloxetine was administered with forced titration decisions occurring at weekly intervals such that the earliest time of maximum dosing to 120 mg/day was three weeks after the first dose. Moreover, on page 227 of the published report of Goldstein 2002 (HMA Q A) it is reported that 75.5% of duloxetine patients were titrated up to the maximum allowed dose of 120 mg/day. In Patel 2011 after two weeks, duloxetine dose was titrated upwards (gradually up to 120 mg/day) if HAM-D score had not decreased more than 50% from baseline.

So, the great majority of included studies (13 out of 16) used duloxetine within the standard therapeutic range (60 to 120 mg/day) and we were not able to carry out this pre-planned subgroup analyses for all head-to-head comparisons:

- Three studies compared duloxetine with escitalopram (Khan 2007 (SCT-MD-23); Nierenberg 2007 (HMCR) and Wade 2007); all were fixed-dose studies and used duloxetine at medium dose (≥ 60 mg but < 90).

- Two studies compared duloxetine with fluoxetine (Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)) and both studies used a flexible dose regimen: no room for subgroup analysis
- Six studies compared duloxetine with paroxetine: all studies used a fixed-dose regimen. We explored the issue about different doses of duloxetine in this subset of trials, but results did not change significantly (see Analysis 75.1).
- Only one study compared duloxetine with desvenlafaxine (Tourian 2009) and quetiapine (Cutler 2009), respectively.
- Two studies compared duloxetine with venlafaxine, but both were flexible-dose regimen studies, so no subgroup analysis could be performed.

2) Comparator dosing: All comparator doses were within the therapeutic range, so it was not considered meaningful to carry out this pre-planned subgroup analysis.

3) Depression severity: The great majority of studies reported a mean baseline score corresponding to moderate to mild major depression. Therefore, it was not meaningful to carry out this pre-planned subgroup analysis.

4) Treatment settings: The great majority of included studies (14 out of 16) recruited outpatients. For only two studies randomised both outpatients and inpatients (Lee 2007 (HMCV); Higuchi 2009a), therefore, it was not considered meaningful to carry out this pre-planned subgroup analysis.

5) Elderly patients: As no study specifically recruited elderly patients, it was not meaningful to carry out this pre-planned subgroup analysis. Four studies included only patients under the age of 65 years (Goldstein 2002 (HMAQ A); Wade 2007; ID#3327 (HMAQ B); Higuchi 2009a) and in the remaining 12 trials, patients of 18 years or older were randomised (in these studies there were some patients over 65 years, but it was not possible to ascertain how many).

FUNNEL PLOT ANALYSIS—As stated in the protocol, analyses were carried out as head-to head comparisons. Where available, the funnel plot analyses did not suggest evidence of publication bias, however, for many comparisons the presence of publication bias was not examined because there were insufficient trials to allow meaningful formal assessment using funnel plots.

SENSITIVITY ANALYSES

1) Excluding trials with unclear concealment of random allocation and/or unclear double blinding: This sensitivity analysis was not performed, because all included studies did not report clear details on concealment of random allocation or blinding.

2) Excluding trials whose dropout rate was greater than 20%: All studies included only patients with unipolar depression, with the exception of Higuchi 2009a which was unclear in terms of possible inclusion of some bipolar patients. Excluding this study, results from the

sensitivity analysis did not materially change the main findings (full details available on request from authors).

3) Performing the worst and best-case scenario analysis: Results from this sensitivity analysis did not materially change the main findings (full details available on request from authors).

4) Excluding trials for which the imputation methods were used

a) Imputed response rate: Imputation methods were not used.

b) Imputed remission rate: Imputation methods were not used.

c) Borrowed SDs: It was not possible to borrow SDs where missing because Cutler 2009 and Tourian 2009 were the only studies comparing duloxetine with quetiapine or desvenlafaxine, respectively.

5) Examination of “wish bias” and exclusion of studies funded by the pharmaceutical company marketing duloxetine: These pre-planned sensitivity analyses were not carried out because we did not find sufficient number of studies not funded by the pharmaceutical company marketing duloxetine.

6) Excluding trials which included patients with bipolar depression: All studies in the present review excluded patients with bipolar disorder (only in one Japanese study was the reporting unclear). Even though it was likely that patients with bipolar disorder were not included in this study, we performed the sensitivity analysis and, as expected, results did not materially change the main findings (full details available on request from authors).

7) Excluding trials which included patients with psychotic features: This sensitivity analysis was not performed, because all included studies did not include patients with psychotic features.

DISCUSSION

Summary of main results

A total of 16 randomised controlled trials (overall 5735 participants) were included in this review. Duloxetine did not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute-phase treatment of major depression. No differences in terms of efficacy were found, even though duloxetine was worse than some SSRIs (most of all, escitalopram) and newer antidepressants (like venlafaxine) in terms of acceptability and tolerability. Unfortunately, we only found evidence comparing duloxetine with a handful of other active antidepressive agents and only a few trials per comparison were found (in some cases we retrieved just one trial). This limited the power of the review to detect moderate, but clinically meaningful differences between the drugs. Moreover, the dataset of the present review collected insufficient randomised evidence to detect a difference in the early response to treatment (after two weeks of treatment). In the absence of clear evidence of an advantage of duloxetine over other antidepressant agents in terms of efficacy or tolerability

and the higher treatment costs per daily dose, duloxetine appears not to be a suitable option as first line treatment for patients with major depression.

Overall completeness and applicability of evidence

It has long been argued that placebo-controlled trials are required to adequately demonstrate the efficacy of novel antidepressant drugs (Cipriani 2009a), however, in the present review we focused only on the comparison between duloxetine and other active treatments. Retrieved randomised evidence compared duloxetine with a selection of possible comparator antidepressants but only a few studies per comparison were found. Although the search was thorough, it is still possible that there are unpublished studies that have not been identified but the small number of trials identified per comparison hinders the detection of any publication bias. Although we did our very best to retrieve as much data as possible, through asking pharmaceutical companies and study authors to supply all available information, we can assume that data from some trials are still lacking, most of which are likely to be studies with negative findings (Turner 2008). We are also aware of the possibility that a number of further randomised controlled trials comparing duloxetine with other antidepressant drugs are currently being conducted and will be included in future updates of the review.

Quality of the evidence

All included studies were RCTs and were very similar in design and conduct. Using high-quality research evidence is relevant to review results and to speed translation of research in a way that really responds to clinically relevant questions. However, the quality of RCTs is not easy to assess. Despite the fact that randomised clinical trials are the best research design to answer questions about efficacy and acceptability of treatments (Cipriani 2009e), the studies included in this review failed to report key methodological issues. For example, the great majority of trials still did not report adequate information about allocation concealment and blinding. The reporting of the outcomes in the included studies was often unclear or incomplete (only graphs, no SDs) and the figures used for the analyses not immediately understandable. The scant information about allocation concealment may be a matter of reporting in the text than real defects in study design. Dealing with summary statistics, the quality of information is important. Meta-analyses of poor quality studies may be seriously misleading (Ioannidis 2005), because the bias associated with defects in the conduct of primary studies (randomised trials) can seriously affect overall estimates of intervention. Systematic review authors (not only within The Cochrane Collaboration) should routinely assess the risk of bias in the results of trials, and should report meta-analyses restricted to trials at low risk of bias (Wood 2008).

Potential biases in the review process

Some possible limitations of this review should be noted.

- Although the search was thorough, it is still possible that there are still unpublished studies which have not been identified.
- The reporting of side effects was different in the included studies (e.g. 2% versus 10% incidence) and this might have affected the pooled estimates.

- By making multiple comparisons we might have committed a type 1 error, that is, identifying and reporting a spurious association. As stated in the review protocol, we did not carry out a Bonferroni correction. As many statistical tests have been used in the review, the findings from this review are better thought of as hypothesis forming rather than hypothesis testing and it would be very comforting to see the conclusions replicated in future trials.
- To assess efficacy we used rating scales scored by clinicians or expert assessors. Even though both HRSD and MADRS are standardised rating scales which are commonly used in antidepressant trials, they are all potentially prone to observer bias. Self-administered questionnaires were not used in the included studies, so this might be a limitation of the methods used in the primary studies of the present review.
- We considered all-cause discontinuation rate as a measure of acceptability of treatment. Even though employed in many other systematic review in the field of antidepressants (Nakagawa 2009; Cipriani 2009b; Omori 2010; Watanabe 2011; Cipriani 2012), this choice might be questioned. We believe early drug discontinuation is highly clinically relevant in the short-term treatment of major depression. Arguably it is one of the most important things the clinician wants to know when starting the prescription of an antidepressant.
- Pharmaceutical industry sponsor. Most of included studies were sponsored by the drug industry, and these have been shown to be more than four times likely to demonstrate positive effects of the sponsors' drug as independent studies (Lexchin 2003). As for all other new investigational compounds, the potential for overestimation of treatment effect due to sponsorship bias should be borne in mind. So, results reported for comparative efficacy have therefore to be viewed with caution because a possible inflation of efficacy in favour of duloxetine cannot be ruled out.
- Economic evaluation. In the present review no RCT reported economic outcomes. Given that several SSRIs and the great majority of antidepressants are now available as generic formulation (only escitalopram and duloxetine are still on patent), more comprehensive economic estimates of antidepressant treatment effect should be considered to better inform healthcare policy.
- In this review we decided to focus on treatment response because it is one of the main goals for the treatment of major depressive disorder. The term "treatment response" describes a state of improvement in the patient's condition of sufficient quality to result in the treating physician's impression of at least a moderate degree of global improvement, conventionally defined as a reduction of at least 50% in depressive symptomatology. However, from a clinical point of view, the ultimate goal of the acute treatment phase of major depressive disorder may well be to achieve remission. Full remission from major depression correlates with better longer-term functional recovery, lower risk of relapse and higher level of patients satisfaction than partial response (without remission). Thus, one important limitation of the included trials (and consequently of the present review) is that

only a few studies reported remission rates, underpowering the analysis and undermining the possibility to find significant differences between comparisons.

- In this review we included only randomised controlled trials (RCTs). As debate in the scientific literature, one of the main limitations of efficacy trials is to include patients far from “real world” (Rothwell 2005). When drafting the systematic review protocol, we did our best to include as much evidence as possible to inform clinical practice, balancing internal with external validity (Cipriani 2009d). In clinical practice, patient populations are usually very heterogeneous, even among groups of patients with the same diagnosis. Proper randomisation and reliable inclusion and exclusion criteria may help create two or more groups that do not differ. However, such groups may be different from others with the same diagnosis, for example because participant selection in many studies is restricted to patients with one typical feature of the disease or to those who happen to be available or willing to participate in the trial. Results from RCTs are average results. In clinical practice, patients need individually tailored treatment. Statistical computations of data from RCTs give clinicians an idea of the probability that the same results would be obtained in other groups of patients with similar clinical characteristics. RCTs are the best way to know which treatment is effective but not necessarily which patients should receive that treatment.

Agreements and disagreements with other studies or reviews

Results from this systematic review are consistent with this interpretation and with current evidence which does not warrant the choice of duloxetine over other new antidepressants based on greater efficacy or safety for patients with acute-phase major depressive disorder (Gartlehner 2009). Even though it is matter of ongoing discussion in the scientific literature (Gartlehner 2010), there is now robust evidence that there are statistically and clinically significant differences among antidepressants (Cipriani 2009a).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review suggest that duloxetine is not better than some other new antidepressant agents in the acute-phase treatment of major depression (especially escitalopram and venlafaxine in terms of acceptability). The present review might contribute to developing and keeping up to date an evidence-based hierarchy of antidepressants to be used by clinicians (both specialists and general practitioners) when prescribing an antidepressant drug for moderate to severe acute major depression.

Implications for research

More randomised controlled trials comparing duloxetine with other antidepressants are needed to generate more precise and accurate information about the drug. Also, randomised controlled trials carried out by independent research institutions and comparing duloxetine with a wider range of active comparators are needed. Furthermore, future studies should focus to a greater extent on outcomes of clear relevance to patients and clinicians, in

particular, patients' and their carers' attitudes to treatment, their ability to return to work and resume normal social functioning. Considering that duloxetine is still on brand, cost-effectiveness issues have also to be assessed.

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External sources

- No sources of support supplied

CHARACTERISTICS OF STUDIES

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

Cutler 2009

Methods	8-week (6-week active-treatment, randomised phase; 2-week post treatment drug-discontinuation/tapering phase), multicentre, double-blind, randomised, parallel-group, placebo- and active-controlled, phase 3 study. Conducted between April 2006 and May 2007	
Participants	Male and female patients with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-defined major depressive disorder. Patients were required to have a 17-item Hamilton rating Scale for Depression (HAM-D) total score higher than or equal to 22 and HAM-D item 1 (depressed mood) score higher than or equal to 2 at enrolment and randomisation Country: US Setting: outpatients Age: 18 to 65 years inclusive	
Interventions	Quetiapine XR 150 mg/day (N = 152); Quetiapine XR 300 mg/day (N = 152); Duloxetine 60 mg/day (N = 151); Placebo (N = 157).	
Outcomes	The primary endpoint was the change from baseline to week 6 in Montgomery-Asberg Depression Rating Scale (MADRS) total score	
Notes	None	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Done. Quote: "... was generated using a computer-based randomization system. Patients were randomly assigned in a 1:1:1:1 manner to one of the four groups: ..."
Allocation concealment (selection bias)	Unclear risk	No information provided.

Blinding (performance bias and detection bias) All outcomes	Low risk	Probably done. Quote: "All packaging of treatments was identical, with placebo and active tablets also identical in appearance, smell, taste, and number."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Probably done. Quote: "For efficacy variables,, a LOCF approach was used for imputation of missing data"
Selective reporting (reporting bias)	Unclear risk	Standard deviations were not reported for continuous outcomes
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Detke 2004 (HMA5 A)

Methods	<p>Multicentre, parallel, double-blind, randomised, placebo- and active comparator-controlled study comparing duloxetine with placebo and paroxetine in the acute and long-term treatment of patients with DSM-IV MDD. The protocol consisted of two identical studies conducted in parallel. Investigators were divided into the two separate study groups prior to beginning the studies. The study consisted of three study periods:</p> <ul style="list-style-type: none"> • Study Period I: A screening phase that lasted 5 to 9 days, during which patients were screened for eligibility. • Study Period II: A 9-week period of acute double-blind treatment. All patients whomet entry criteria were enrolled and placed on placebo at Visit 2 (for a period of 1 week). At Visit 3, patients were randomly assigned to one of four treatment groups: duloxetine 60 mg BID, duloxetine 40 mg BID, placebo, or paroxetine 20 mg QD. At Visit 8, patients either concluded their participation in the study, or continued into Study Period III. • Study Period III: A long-term period (28-week) of continuation double-blind treatment (26 weeks of active treatment; 2 weeks of placebo lead-out). All patients who continued into this phase remained in the same treatment group to which they were randomly assigned at Visit 3. At Visit 15, all patients transitioned to placebo. Patients received placebo from Visit 15 to Visit 16
Participants	<p>Male and female patients with a primary diagnosis of major depression as defined by the DSM-IV. Patients were required to have a HAM-D17 total score ≥ 15 and a CGI-Severity total score ≥ 4 at both Visits 1 and 2 Country: unclear Setting: outpatients Age: at least 18 years of age</p>
Interventions	<p>Duloxetine 60 mg BID (120 mg/day) Duloxetine 40 mg BID (80 mg/day) Paroxetine 20 mg QD (20 mg/day) Placebo Duration: 34 weeks active treatment with 1-week placebo lead-in period and 2-week placebo lead-out period</p>
Outcomes	<p>Efficacy: Primary efficacy measure was the HAM-D17 total score. Secondary efficacy measures included HAM-D17 response rates (a 50% reduction from baseline to endpoint) and HAM-D17 remission rates (endpoint score ≤ 7). Other secondary measures included the HAM-D17 subscales and individual items, MADRS, CGI-Severity, PGI-Improvement, HAM-A, SSI, and VAS for pain. The SDS and healthcare resource utilisation costs were also included for health outcomes analysis Safety: Safety was evaluated through the collection and reporting of discontinuation rates, treatment emergent adverse events, discontinuation-emergent adverse events, laboratory analyses, vital signs, ECGs, and the ASEX</p>

Notes Date of first patient enrolled: 16 November 2000
 Date of last patient completed: 22 July 2002
 Statistical Methods: All analyses were conducted on an intent-to-treat basis unless otherwise specified. Treatment effects were evaluated based on a two-sided significance level of .05. No adjustments for multiple comparisons were made. For all total scores calculated from individual items, if any of the individual items were missing, the corresponding total score was considered missing. Continuous efficacy data were analysed using likelihood-based repeated measures analyses. Patients were not selected for the presence, type, or severity of pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "patients were randomly assigned in a 1:1:1:1 ratio to placebo, duloxetine 80 mg/day, duloxetine 120 mg/day or paroxetine 20 mg/day"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "treatments were administered in a double blinded fashion via the use of a double dummy study drug design"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Probably done. Quote: "All analyses were conducted on an Intention-to-treat (ITT) basis. (...)The change from baseline to endpoint in the HDRS- 17 item total score and other continuous efficacy variables were also calculated using LOCF"
Selective reporting (reporting bias)	Unclear risk	In the duloxetine 120 mg/day arm only treatment emergent side effects experienced by > or = 5% of patients are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Goldstein 2002 (HMAQ A)

Methods	Multicentre, parallel, double-blind, randomised, placebo-controlled outpatient study. Fluoxetine was used as an active comparator to determine whether the study design was sensitive to the effects of a known selective serotonin reuptake inhibitor (SSRI) antidepressant. Patients who met entry criteria in Study Period I were randomly assigned to one of the following three treatment groups: duloxetine 20 mg to 60 mg BID, fluoxetine 20 mg once daily (QD), or placebo. This study employs a variable-duration, double-blind, placebo lead-in period. Patients were treated in a double-blind manner for 10 weeks (Study Period II, Visits 2-12). Active therapy ended at Visit 11 and was then followed by a double-blind placebo lead-out week from Visit 11 to Visit 12. Study Period III consisted of a post-therapy, study drug discontinuation phase. The protocol consisted of two identical studies conducted in parallel and reported separately (Study Group A and Study Group B)
Participants	Male and female patients who met DSM-IV criteria for nonpsychotic major depression single episode or recurrent, confirmed by the Mini International Neuropsychiatric Interview (MINI) with a current episode duration of ≥ 2 weeks. Patients were at least moderately depressed as defined by a CGI-Severity scale score ≥ 4, and had a HAM-D17 total score ≥ 15 at Visits 1 and 2 Country: unclear Setting: outpatients Age: 18 to 65 years inclusive
Interventions	Duloxetine 20 mg to 60 mg BID (40 to 120 mg/day) Fluoxetine 20 mg QD (20 mg/day) Placebo
Outcomes	Efficacy: Primary efficacy measure was the mean change from baseline to endpoint on the clinician-rated HAM-D17. Secondary efficacy measures included response rates (a 50% reduction from baseline to endpoint) and remission rates (endpoint score ≤ 7) on the HAM-D17, MADRS, HAM-A, CGI-S, CGI-I, PGI-Improvement, and HAM-D17 sub-factor scores

Safety: Safety was evaluated through the collection and reporting of discontinuation rates, treatment-emergent adverse events, laboratory analyses, vital signs, and the ASEX Scale
Health Outcomes: Quality of life was evaluated using the SF-36

Notes
Date first patient enrolled: 11 February 1999
Date last patient completed: 23 May 2000
For the primary analysis, all study sites with fewer than 10 randomly assigned patients were pooled together and considered as a single site. If this resulted in a site with fewer than 10 randomly assigned patients, these patients were pooled with the next smallest site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "Patients were randomly allocated to placebo, duloxetine or fluoxetine treatments groups in a 2:2:1 ratio"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind (...). The number of capsules administered daily (4 capsules every morning, 3 capsules every evening) was consistent among groups"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Efficacy outcome both continuous or categorical, were analysed using a mixed effects likelihood-based repeated-measures (MMRM) analysis"
Selective reporting (reporting bias)	Unclear risk	In duloxetine arm only adverse events that have an incidence > 10% were reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Goldstein 2004 (HMAT B)

Methods	Multicentre, parallel, double-blind, randomised, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out. The protocol consisted of two identical studies conducted in parallel and reported separately (Study Group A and Study Group B). The study consisted of two study periods. Study Period I was the 1-week screening phase of the study, and Study Period II was an 11-week acute therapy phase in which patients were assessed weekly from Visit 2 (Week 0) to Visit 5 (Week 3) and every other week from Visit 5 (Week 3) to Visit 9 (Week 11). This study design employed double-blind, variable-duration placebo lead-in and lead-out periods to blind patients and investigators at the start and end of active therapy
Participants	Male and female patients with a primary diagnosis of MDD as defined by the DSM-IV, and confirmed by use of the MINI. Patients were required to have a HAM-D17 total score ≥ 15 and a CGI-S total score ≤ 4 at both Visit 1 and Visit 2 Country: US Setting: outpatients Age: at least 18 years of age
Interventions	Duloxetine 20 mg BID (40 mg/day) Duloxetine 40 mg BID (80 mg/day) Paroxetine 20 mg QD (20 mg/day) Placebo
Outcomes	Efficacy: The primary efficacy measure was the HAM-D17 total score. Secondary efficacy measures included HAM-D17 response rates (50% reduction from baseline to endpoint), HAM-D17 remission rates (endpoint score ≤ 7), time to sustained response, and time to sustained remission. Other secondary measures included the HAM-D17 subfactors and individual items, MADRS, CGI-S, PGI-I, HAM-A, Somatic Symptom Inventory 26- and 28-item scale, and VAS for pain Safety: Safety was evaluated through the collection and reporting of discontinuation rates, treatment-emergent adverse events, discontinuation-emergent adverse events, laboratory analyses, vital signs, ECGs, and the ASEX

Health Outcomes: Health outcomes were evaluated using the QLDS scale and Health Resource Utilisation scales

Notes Date first patient enrolled: 09 March 2000
Date last patient completed: 06 February 2001
Sites with fewer than 8 randomly assigned patients with baseline and at least one post-baseline (Visit 4 to Visit 8) HAM-D17 total score were pooled. If this resulted in a pooled site with fewer than 8 patients, these patients were pooled with the next smallest site

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were allocated within each study site by a computer-generated random table and had an equal probability of receiving placebo, duloxetine 40 mg/day, administered as 20 mg twice daily, duloxetine 80 mg/day, administered as 40 mg twice daily, or paroxetine 20 mg/day administered once daily during the 8 week acute therapy phase. No stratification was employed"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "All treatments were administered in a blinded fashion. The blind was maintained throughout the study using capsules identical in appearance for both study drug and placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "all analyses were conducted on an ITT basis. Longitudinal efficacy outcomes were primarily analysed using a MMRM approach"
Selective reporting (reporting bias)	Unclear risk	Quote: "Treatment emergent adverse events experience by at least 5% of patients treated with duloxetine 80 mg/day and statistically significantly different from placebo are reported"
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Higuchi 2009a

Methods	This was a multicentre, parallel, double-blind, randomised, placebo- and active comparator-controlled study comparing duloxetine with placebo and paroxetine in the acute treatment of patients with DSM-IV MDD
Participants	Male and female patients with a primary diagnosis of MDD as defined by the DSM-IV, and confirmed by use of the MINI. Patients were required to have a HAM-D17 total score ≥ 15 and a CGI-S total score ≥ 4 at both Visit 1 and Visit 2 Country: Japan Setting: inpatients and outpatients Age: 18 to 65 years inclusive
Interventions	Duloxetine 40 mg/day, once in the morning Duloxetine 60 mg/day, once in the morning Paroxetine 20-40 mg/day, once in the evening Placebo Duration: 6 weeks active treatment with 1-week placebo lead-in and 2-week lead-out periods Cointervention: No psychotropic drug except for one short or ultra-short acting benzodiazepine sleeping pill
Outcomes	Efficacy: Primary efficacy measure was the HAM-D17 total score. Secondary efficacy measures included HAM-D17 response rates (a 50% reduction from baseline to endpoint) and HAM-D17 remission rates (endpoint score < 7), VAS for pain, CGI-I
Notes	Randomised: 495 patients, however the first 50 patients were randomised according to a wrong randomisation scheme and were therefore omitted from the main analyses. The correct ITT sample

would then be: 75 for duloxetine 40 mg, 76 for duloxetine 60 mg, 148 for paroxetine and 146 for placebo

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "The sequence was generated by an independent investigator."
Allocation concealment (selection bias)	Low risk	Probably done. Quote: "The allocation was handled by an independent investigator."
Blinding (performance bias and detection bias) All outcomes	Low risk	Both the clinician and the patient were blinded. The capsules have been tested to be indistinguishable. The clinician was the assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 445 patients appropriately randomised, 5 patients did not contribute at all to the analysis and about 10% of the patients had to have their outcomes LOCFed (the exact numbers cannot be known due to the way the authors summarised the data.)
Selective reporting (reporting bias)	Unclear risk	The protocol has not been published and we do not know if all the intended outcomes are reported
Other bias	Low risk	5-armed placebo- and active drug-controlled trial appears more trustworthy than straightforward 2-arm trial

ID#3327 (HMAQ B)

Methods	Multicentre, parallel, double-blind, randomised, placebo-controlled outpatient study. Fluoxetine was used as an active comparator to determine whether the study design was sensitive to the effects of a known selective SSRI antidepressant. Patients who met entry criteria in Study Period I were randomly assigned to one of the following three treatment groups: duloxetine 20 mg to 60 mg BID, fluoxetine 20 mg once daily (QD), or placebo. All patients received placebo for the first week (from Visit 2 to Visit 3). Patients were treated in a double-blind manner for 10 weeks (Study Period II, Visits 2-12). Active therapy ended at Visit 11 and was then followed by a double-blind placebo lead-out week from Visit 11 to Visit 12. Study Period III consisted of a post-therapy, study drug discontinuation phase. The protocol consisted of two identical studies conducted in parallel and reported separately (Study Group A and Study Group B)
Participants	Male and female outpatients aged 18 to 65 years who met DSM-IV criteria for nonpsychotic major depression single episode or recurrent, confirmed by the MINI with a current episode duration of 2 weeks. Patients were at least moderately depressed as defined by a CGI-S scale score 4, and had a HAM-D17 total score 15 at Visits 1 and 2 Country: US Setting: outpatients Age: 18 to 65 years inclusive
Interventions	Duloxetine 20 mg to 60 mg BID (40 to 120 mg/day) Fluoxetine 20 mg QD (20 mg/day) Placebo
Outcomes	Efficacy: Primary efficacy measure was the mean change from baseline to endpoint on the clinician-rated HAM-D17. Secondary efficacy measures included response rates (a 50% reduction from baseline to endpoint) and remission rates (endpoint score 7) on the HAM-D17, MADRS, HAM-A, CGI-Severity, CGI-I, PGI-I, and HAM-D17 subscale scores. Safety: Safety was evaluated through the collection and reporting of discontinuation rates, treatment-emergent adverse events, laboratory analyses, vital signs, and the ASEX Health Outcomes: Quality of life was evaluated using the SF-36
Notes	Date first patient enrolled: 10 March 1999 Date last patient completed: 04 January 2001

For the primary analysis, all study sites with fewer than 10 randomly-assigned patients were pooled together and considered as a single site. If this resulted in a site with fewer than 10 randomly-assigned patients, these patients were pooled with the next smallest site

Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "180 patients randomly assigned 2:2:1 to duloxetine, placebo, fluoxetine"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Probably done. Quote: "Patients were treated in a double blind manner"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "An ITT principle was applied in all efficacy and safety analyses"
Selective reporting (reporting bias)	Unclear risk	Only adverse effects with total incidence > or = 2% are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

ID#4091 (HMAT A)

Methods	This study was a multicentre, parallel, double-blind, randomised, placebo- and active comparator-controlled study with a blinded placebo lead-in and placebo lead-out. The protocol consisted of two identical studies conducted in parallel and reported separately (Study Group A and Study Group B (published as Goldstein 2004)). The study consisted of two study periods; Study Period I was the 1-week screening phase, and Study Period II was an 11-week acute therapy phase in which patients were assessed weekly from Visit 2 to Visit 5 and every other week from Visit 5 to Visit 9. This study design employed double-blind, variable-duration placebo lead-in and lead-out periods to blinded patients and investigators at the beginning and end of active therapy
Participants	Male and female patients with a primary diagnosis of MDD as defined by the DSM-IV, and confirmed by use of the Mini International Neuropsychiatric Interview. Patients were required to have a HAM-D17 total score of ≥ 15 and a CGI-S total score of ≥ 4 at both Visit 1 and Visit 2 Country: US Setting: outpatients Age: at least 18 years of age
Interventions	Duloxetine 20 mg BID (40 mg/day) Duloxetine 40 mg BID (80 mg/day) Paroxetine 20 mg QD (20 mg/day) Placebo
Outcomes	Efficacy: The primary efficacy measure was the HAM-D17 total score. Secondary efficacy measures included HAM-D17 response rates (a 50% reduction from baseline to endpoint), HAM-D17 remission rates (endpoint score of ≤ 7), time to sustained response, and time to sustained remission. Other secondary measures included the HAM-D17 subfactors and individual items, MADRS, CGI-Severity, PGI-Improvement, HAM-A, Somatic Symptom Inventory, and VAS for pain. Safety: Safety was evaluated through the collection and reporting of discontinuation rates, TEAEs, discontinuation-emergent adverse events, laboratory analyses, vital signs, ECGs, and the ASEX. Health Outcomes: Health outcomes were evaluated using the Quality of Life in Depression scale and Health Resource Utilisation scales
Notes	Date first patient enrolled: 10 March 2000 Date last patient completed: 10 April 2001 For all total scores calculated from individual items, if any of the individual items was missing, the corresponding total score was considered missing. Sites with fewer than 8 randomly assigned patients with baseline and at least one post-baseline (Visit 4 to Visit 8) HAM-D17 total score were

pooled. If this resulted in a pooled site with fewer than 8 patients, these patients were pooled with the next smallest site

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Probably done. Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "ITT principle was applied in all efficacy and safety analyses"
Selective reporting (reporting bias)	Unclear risk	Only adverse effects with total incidence > or = 2% are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

ID#7999 (HMCQ)

Methods	Multicentre, randomised, double-blind, parallel, outpatient study with DSM-Fourth Edition (DSM-IV)-defined major depressive disorder. Patients who met entry criteria in Study Period I (3-9 days, no treatment) were randomly assigned to one of the following two treatment groups: duloxetine 60 mg/day, venlafaxine 75 mg/day or venlafaxine 150 mg/day (patients randomised for the first 2 weeks and then venlafaxine could be titrated up to 150 mg/day for the remaining 4 weeks, if necessary. In Study Period III (between week 6 to week 12) duloxetine could be titrated up to 90 or 120 mg/day and venlafaxine up to 225 mg/day (doses could be maintained at the previous levels at the discretion of the investigator). Study Period IV consisted of a tapering off phase
Participants	Male or female patients who meet criteria for MDD as defined by DSM-IV criteria and confirmed by the MINI. HDRS (HAM-D17) total score 18 at Visit 1 Country: unclear Setting: outpatients Age: at least 18 years of age
Interventions	Duloxetine: 60 to 120 mg daily, given orally. Venlafaxine extended release: 75 to 225 mg daily, given orally
Outcomes	Efficacy: The primary outcome assessment of duloxetine 60 mg QD compared with venlafaxine extended release 150 mg QD in the treatment of MDD was based on a GBR analysis of the HAM-D17 total score and the Association of Methodology of Documentation in Psychiatry-Module 5 (AMDP-5) results collected from Study Period II. These data were combined with the data from similarly designed Study HMBU, as specified a priori in the protocol. The primary efficacy measure was the HAM-D17 total score. Secondary measures included HAM-D17 subscales (Core, Maier, Anxiety/Somatisation, Retardation/Somatisation, and Sleep) and depressed mood item (Item 1); HAM-D17 response and remission; HAM-A; CGI Severity) Patient's Global Impressions of Improvement (PGI-I); time to the first visit that a sustained 30% improvement on the HAM-D17 Maier subscale was achieved; time to the first visit that the HAM-D17 total score was 7; and cognitive composite score. Secondary assessments were the GBR analysis of results from Study Periods II and III combined and the HAM-D17 noninferiority analysis (data for these assessments were combined with data from Study HMBU, as specified a priori in the protocol). Safety: Safety measures included serious adverse events, adverse events reported as the reason for discontinuation, treatment-emergent adverse events, vital signs, electrocardiograms, laboratory analytes, adverse events from the AMDP-5, Change in Sexual Function Questionnaire (CSFQ), and the Pittsburgh Sleep Quality Index (PSQI).

Health Outcomes: Health outcome measures reported in this study were the 36-item Short Form Health Survey (SF-36), Quality of Life in Depression Scale, Euro-QOL Questionnaire-5 Dimension (EQ-5D), and the SDS

Notes	Date of first patient enrolled: 14 July 2003 Date of last patient completed: 30 March 2004	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Probably done. Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All analyses were conducted on ITT analysis".
Selective reporting (reporting bias)	Unclear risk	Only Adverse Events with total incidence > or = 5% are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Khan 2007 (SCT-MD-23)

Methods	Study SCT-MD-23 was a multicentre, randomised, double-blind, parallel-group, 8- week study followed by a double-blind, 1-week down-titration period (for patients who did not continue into Study SCT-MD-23A). Patients who completed Study SCT-MD-23 were eligible to continue double-blind treatment at the same dose they received at the completion of Study SCT-MD-23 for an additional 16 weeks in Study SCT-MD-23A, followed by a double-blind, 1-week down-titration period	
Participants	Male and female patients, meeting DSM-IV criteria for MDD and having a minimum total score of 26 on MADRS Country: US Setting: outpatients Age: 18 to 80 years of age	
Interventions	Escitalopram: 10 to 20 mg/d Duloxetine: 60 mg/d	
Outcomes	The primary parameter in Study SCT-MD-23 was the change from baseline to Week 8 in MADRS total score using the LOCF approach	
Notes	Date of first patient enrolled: 12 April 2005 Date of last patient completed: 10 March 2006	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Patients were randomly assigned to receive 8 weeks of double blind treatment with either escitalopram or duloxetine

Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “8 weeks double blind treatment (...) dose titration was achieved using a double dummy design; all patients received two capsules up to week 4, and two or three thereafter”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “Efficacy analysis was based on an ITT population”.
Selective reporting (reporting bias)	Unclear risk	Only adverse effects occurring in at least 10% of patients in either treatment group are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Lee 2007 (HMCV)

Methods	This was a multi-country/region, randomised, double-blind, double-dummy, parallel, active treatment-controlled trial with three study periods. Patients (in both in- and outpatients) aged 18 years and older who met the DSM-IV criteria for major depressive disorder (MDD) were randomised to one of two treatment groups: duloxetine 60mg/day or paroxetine 20 mg/day. Following the screening phase (Study Period I), participants were treated in a double-blind manner for approximately 8 weeks (Study Period II). A double-blind taper period was then conducted in order to assess and minimize the discontinuation symptoms that may occur while stopping duloxetine or paroxetine (Study Period III)
Participants	Patients of either sex who met the DSM-IV criteria for nonpsychotic MDD, and had a HAM-D17 total score ≥ 15 and CGI-S score ≥ 4 were included Country: China, Korea, Taiwan and Brazil Setting: inpatients and outpatients Age: at least 18 years of age
Interventions	Duloxetine: 60 mg/day (given orally once a day as two 30 mg capsules). Paroxetine: 20 mg/day, given orally once a day as two 10 mg capsules
Outcomes	Efficacy: The primary measure of efficacy was to assess the severity of depression and its improvement during the course of therapy, using the HAM-D17. Secondary measures of efficacy included: presence and severity of anxiety (HAM-A), severity of illness (CGI-S) degree of improvement (PGI-I, degree to which physical complaints were bothersome to patient (SSI), and experience of overall pain (VAS). Safety: Assessment of adverse events, including serious adverse events, routine laboratory tests, vital signs, and ECGs
Notes	For the primary efficacy analysis, a one-sided 97.5% confidence interval of the adjusted mean HAM-D17 total score was used to determine whether duloxetine was non inferior to paroxetine. Noninferiority was declared if the upper bound of the one-sided 97.5% confidence interval was less than 2.2 Date of first patient enrolled: 17 February 2004. Date of last patient completed: 12 June 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients meeting the entry criteria were randomized in a ratio of 1:1 to either duloxetine 60mg/day or paroxetine 20mg/day”
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance)	Unclear risk	Probably done “double blind”.

bias and detection bias) All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “The primary analysis based on a per-protocol population was also supported in the ITT population”
Selective reporting (reporting bias)	Unclear risk	Only adverse events occurring with frequency > or = 5% are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Nierenberg 2007 (HMCR)

Methods	This study was a multicentre, 8-month, randomised, active- and placebo-controlled, double-blind trial with two study periods for the evaluation of comparative efficacy between duloxetine, escitalopram, and placebo in patients with major depression. During study period II, the first 8 weeks were considered the acute phase: fixed-dose comparison of duloxetine 60 mg QD, escitalopram 10 mg QD, and placebo. After the first 8 weeks, patients continued in a flexible-dose extension phase (for up to 6 months) in which duloxetine doses could be increased to 120 mg QD with 90 mg QD as an intermediate dose, and escitalopram doses could be increased to 20 mg QD
Participants	Study patients included male or female patients who met DSM-IV criteria for major depression. Additionally, patients must have had a CGI-S score ≤ 4 and a MADRS total score ≤ 22 at screening and baseline visits Country: US Setting: outpatients Age: at least 18 years of age
Interventions	During the acute treatment phase of this study, patients were randomised to one of three fixed-dose study-drug therapy groups: duloxetine 60 mg/day, escitalopram 10 mg/day, or placebo. All study drugs were given orally, once daily. During the extension phase of this study, the dosage of duloxetine could be increased to 90 and then to 120 mg/day; and the dosage of escitalopram could be increased to 20 mg/day
Outcomes	Efficacy: The primary outcome was assessed by the percentage of patients who achieved a 20% decrease in the Maier subscale (Items 1, depressed mood; 2, guilt; 7, work and activities; 8, retardation; 9, agitation; and 10, psychic anxiety) of the HAM-D17 that was maintained or exceeded at all subsequent visits throughout acute treatment. Secondary efficacy measures included HAM-D17 total score and subscores, CGI-S scale for mental illness, PGI-I scale emotional, and HAM-A total score and subscores Safety and tolerability: Safety and tolerability were evaluated through the collection and reporting of discontinuation rates, serious adverse events, TEAEs, and changes in sexual functioning (based on the Changes in Sexual Functioning Questionnaire (CSFQ)), laboratory analyses, and vital signs Health Outcomes: Health outcomes were assessed by mean changes from baseline on the SDS, EWPS, and the Q-LES-Q-SF, as well as categorical changes in satisfaction with study drug therapy
Notes	No adjustments for multiple comparisons were made. For all total scores calculated from individual items, if any of the individual items were missing, the corresponding total score was considered missing. Onset of antidepressant action was analysed primarily with a pseudo-likelihood based categorical repeated measures approach and, secondarily, with a Kaplan-Meier survival analysis. Continuous data were analysed using likelihood-based repeated measures analyses, and with analysis of variance with missing values inputted using the last-observation-carried-forward approach Date first patient entered study: 26 November 2003 Date last patient completed: 06 May 2005

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Patients meeting entry criteria were randomly assigned in a 2:2:1 fashion to either duloxetine or escitalopram, or placebo via the Interactive Voice Response System (IVRS)”
Allocation concealment (selection bias)	Unclear risk	No information provided.

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Placebo capsules and matching duloxetine and escitalopram capsules were utilized in double-dummy fashion to maintain the integrity of the blind during the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All analyses were conducted in a ITT basis.
Selective reporting (reporting bias)	Unclear risk	Only MMRM data available. Only adverse events occurring with frequency > or = 5% are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Patel 2011

Methods	A total of 13 centres across India participated in this open label, randomised, comparative, parallel group, multi-centric study to evaluate the safety and efficacy of duloxetine compared with venlafaxine in patients of MDD. The present study has been conducted between June 2003 to April 2005	
Participants	Male or female patients with diagnosis of DSM IV or ICD 10 MDD with a total score of at least 15 on HDRS were enrolled in the study for 6 weeks. Newly diagnosed, non-responders or partial responders to the prescribed antidepressants, not tolerating prescribed antidepressants patients were included. Participants with evidence/ history of recent significant clinical disorder (or clinically significant abnormal laboratory finding), schizoaffective or bipolar disorder, seizure disorder or current / prior diagnosis of anorexia nervosa, chronic history/behavior of suicide, concurrent major illness or systemic dysfunction involving hepatic and renal systems, therapy with lithium within the preceding month, alcohol or drug abuse, currently receiving cimetidine, warfarin, tryptophan or MAO inhibitors and history of allergy to duloxetine and venlafaxine, non responder to venlafaxine, participation in any drug trial within 4 weeks were excluded. Pregnant women, lactating mothers, women in child bearing age, not using contraceptives or desiring to have children were also excluded Country: India Setting: unclear Age: patients aged between 18-65 years	
Interventions	Duloxetine (flexible dose regimen): 20 mg BID (40 mg/day) to 60 mg BID (120 mg/day) Venlafaxine (flexible dose regimen): 75 mg/day to 225 mg/day	
Outcomes	Primary Efficacy parameters: 1) Comparison of HAM-D total score (The sum of all 17 items); 2) Comparison of MADRS total score (The sum of all 10 items) Secondary Parameters: 1) CGI -S score and CGI -I score; 2) Response rate at end of week 4 & week 6.	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Probably done. Quote: "...randomized to any of the two treatment groups as per randomization schedule."
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-design study but no details provided on outcome assessments (the primary outcome is HAM-D mean endpoint score and a blind-to-treatment outcome assessor would be needed)

Incomplete outcome data (attrition bias) All outcomes	High risk	No information is reported on how to deal with incomplete outcome data and no SDs are provided
Selective reporting (reporting bias)	High risk	No information at all reported on such an important issue
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Perahia 2006 (HMA Y B)

Methods	Multicentre, parallel, double-blind, randomised, placebo-and active comparator-controlled study with blinded placebo lead-in and placebo lead-out. Acute treatment lasted 8 weeks, followed by a 26-week continuation phase for responders
Participants	Patients with a primary diagnosis of major depression as defined by the DSM-IV. Patients were required to have a HAM-D17 total score ≥ 15 and a CGI-S total score ≤ 4 at both Visits 1 and 2 Country: Bulgaria, Croatia, Hungary, Poland, Romania, Russia, and Slovakia Setting: outpatients Age: patients aged 18 years or more
Interventions	Duloxetine 40 mg BID (80 mg/day) Duloxetine 60 mg BID (120 mg/day) Paroxetine 20 mg QD (20 mg/day) Placebo
Outcomes	Efficacy: Primary efficacy measure was the HAM-D17 total score. Secondary efficacy measures included HAM-D17 response rates (a 50% reduction from baseline to endpoint), and HAM-D17 remission rates (endpoint score ≤ 7). Other secondary measures included the HAM-D17 subscales and individual items, MADRS, CGI-Sy, PGI-I, HAM-A, SSI, and VAS for pain. The SDS and healthcare resource utilisation were also included for health outcomes analysis Safety: Safety was evaluated through the collection and reporting of discontinuation rates, TEAEs, discontinuation-emergent adverse events, laboratory analyses, vital signs, ECGs, and the ASEX
Notes	No adjustments for multiple comparisons were made. For all total scores calculated from individual items, if any of the individual items were missing, the corresponding total score was considered missing. Continuous efficacy data were analysed using likelihood-based, repeated measures analyses Date of first patient enrolled: 31 October 2000 Date of last patient completed: 4 July 2002

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: Patients were randomly assigned in a 1:1:1:1 ratio to placebo, duloxetine 80 mg/day, duloxetine 120 mg/day or paroxetine 20 mg/day"
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Treatments were administered in a double blind fashion via the use of a double dummy study drug design"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All analyses were conducted on an ITT basis".
Selective reporting (reporting bias)	Unclear risk	In duloxetine 120 mg/day group only adverse events with an incidence $\geq$ or $\leq$ 2.5% are reported

Other bias Unclear risk Sponsorship bias cannot be ruled out.

Perahia 2008 (HMBU)

Methods	Multicentre, randomised, double-blind, parallel, outpatient study. Patients who met entry criteria in Study Period I (3-9 days, no treatment) were randomly assigned to one of the following two treatment groups: duloxetine 60 mg/day or venlafaxine 75 mg/day for the first 2 weeks and then 150 mg/day for the remaining 4 weeks. In Study Period III (between week 6 to week 12) duloxetine could be titrated up to 90 or 120 mg/day and venlafaxine up to 225 mg/day (doses could be maintained at the previous level at the discretion of the investigator). Study Period IV consisted of a tapering off phase
Participants	Male or female patients who met DSM-IV criteria for MDD confirmed by the Mini International Neuropsychiatric Interview. HAM-D17 total score 18 at Visit 1 Country: US and Canada Setting: outpatients Age: patients aged 18 years or more
Interventions	Duloxetine: 60 to 120 mg daily, given orally. Venlafaxine extended release: 150 to 225 mg daily, given orally
Outcomes	Efficacy: The primary outcome assessment of duloxetine 60 mg QD compared with venlafaxine extended release 150 mg QD in the treatment of MDD was based on a global benefit-risk (GBR) analysis of the HAM-D17 total score and the Association of Methodology of Documentation in Psychiatry-Module 5 (AMDP-5) results collected from Study Period II. These data were combined with data from the similarly designed Study HMCQ, as specified a priori in the protocol. The GBR assessment approach was first proposed by Chuang-Stein et al. (1991). In this assessment, benefit was defined as remission at endpoint (HAM-D17 total score 7), a virtually symptom-free state. Risk was defined by four categories: no AMDP-5- collected adverse events (AMDPAE), mild or moderate AMDPAE, severe AMDPAE, and discontinued with a reason of self-reported adverse event. The primary efficacy measure was the HAM-D17 total score. Secondary efficacy measures included the HAM-D17 subscales (Core, Maier, Anxiety/Somatization, Retardation/Somatization, and Sleep) and depressed mood item (Item 1); HAM-D17 response and remission; HAM-A; CGI-S; PGI-I; time to the first visit that a sustained 30% improvement on the HAM-D17 Maier subscale was achieved; time to the first visit that the HAM-D17 total score was 7; and cognitive composite score. Secondary assessments were the GBR analysis of results from Study Periods II and III combined and the HAM-D17 non-inferiority analysis (data for these assessments were combined with data from Study HMCQ, as specified a priori in the protocol). Safety: Safety measures included serious adverse events (SAEs), adverse events reported as the reason for discontinuation, treatment-emergent adverse events, vital signs, electrocardiograms, laboratory analytes, adverse events from the AMDP-5, CSFQ and the PSQI. Health Outcomes: Health outcome measures reported in this study were the 36-item Short Form Health Survey (SF-36), Quality of Life in Depression Scale, Euro-Qol Questionnaire-5 Dimension (EQ-5D), and the SDS
Notes	Date of first patient enrolled: 01 August 2003 Date of last patient completed: 11 May 2004 The primary objective of this study was to test the hypothesis that duloxetine 60 mg QD is statistically significantly superior to venlafaxine extended release 150 mg QD during the 6 weeks of Study Period II using a global benefit-risk (GBR) assessment in outpatients with DSM-IV-defined major depressive disorder. Data from HMBU and the similar study ID#7999 (HMCQ) were pooled as defined a priori in the study protocols for the purposes of the primary and other objectives. The secondary objectives of the study included: <ul style="list-style-type: none"> To test the hypothesis that duloxetine 60 mg daily was not inferior to venlafaxine extended release 150 mg daily during 6 weeks of therapy, and that duloxetine 60 to 120 mg was not inferior to venlafaxine extended release 150 to 225 mg during 12 weeks of therapy, in the efficacy of treating MDD as measured by the mean change from baseline to endpoint on the HAM-D17 total score. Data from this study and a similar study, ID# 7999 (HMCQ), were combined for this comparison. To test the hypothesis that duloxetine 60 to 120 mg daily was statistically significantly superior to venlafaxine extended release 150 to 225 mg daily during 12 weeks of therapy using global benefit-risk assessment. Data from this study and a similar study, ID#7999 (HMCQ), were combined for this comparison
Risk of bias	
Bias	Authors' judgement Support for judgement

Random sequence generation (selection bias)	Low risk	Probably done. Quote: "randomized".
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Probably done. Quote: "Double blind".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "All analyses were conducted on ITT analysis".
Selective reporting (reporting bias)	Unclear risk	Only Adverse Events with total incidence > or = 5% are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Tourian 2009

Methods	This was an 8-week, Phase III, randomised, double blind, placebo-controlled, parallel-group trial conducted from September 2006 to September 2007 in 21 centres across the United States. After an initial screening period of 6 to 14 days, eligible patients were randomly assigned to treatment for 8 weeks plus 1 additional week for tapering the study medication. The 7-day taper period was recommended, but could be omitted, shortened, or lengthened at the discretion of the investigator. Patients returned for a follow-up visit ~7 days after the last dose of the study medication
Participants	Male and female patients with a primary diagnosis of MDD. At screening, a psychiatric assessment was performed by the investigator using a modified Mini International Neuropsychiatric Interview and a diagnosis of MDD-single or recurrent episode without psychotic features-was confirmed according to DSM-IV criteria. Patients were required to have depressive symptoms for at least 30 days before the screening visit. The following minimum scores were required at screening and baseline: 17-item Hamilton Rating Scale for Depression (HAM-Dp) total score of at least 20; HAM-D17 item 1 (depressed mood) score of at least 2; and CGI-S score of at least 4 (moderately ill). All sexually active patients in the study were required to use medically acceptable contraception. Exclusion criteria included previous treatment with desvenlafaxine; known hypersensitivity to venlafaxine; significant risk of suicide based on clinical judgment; pregnancy or breastfeeding; current psychoactive substance abuse or dependence, manic episode, posttraumatic stress disorder, obsessive-compulsive disorder, or a lifetime diagnosis of bipolar or psychotic disorder; current primary generalized anxiety disorder, panic disorder, social anxiety disorder, or clinically important personality disorder; depression associated with the presence of an organic mental disorder; history of seizure disorder; clinically important medical disease; or use of prohibited treatments, including use of venlafaxine (immediate or extended release) and duloxetine within 90 days of baseline, investigational drugs, antipsychotics, fluoxetine within 30 days of baseline, or anxiolytics and other antidepressants within 14 days of baseline Country: US Setting: outpatients Age: patients aged 18 years or more
Interventions	A total of 155 patients were randomly assigned to receive desvenlafaxine 50 mg/d; 160, desvenlafaxine 100 mg/d; 159, duloxetine 60 mg/d; and 164, placebo
Outcomes	The primary efficacy measure, the HAM-D17, was administered at screening, baseline, and each visit of the on-treatment period (weeks 1,2,3,4, 6, and 8). Secondary efficacy measures included the CGI-I17 score, which was rated from 1 (very much improved) to 7 (very much worse) and administered at each visit of the on-treatment period. Other secondary efficacy measures included the MADRS total scores, CGI-S scores, the 6-item HRSD, Bech version (HAM-D6) (Bech version: HAM-D17 items 1,2, 7, 8, 10, and 13) , remission rates (defined as a HAM-D17 score less than 7), and responder rates (defined as a decrease from baseline of at least 50% in HAM-D17 total score)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Allocation of patients to study groups proceeded through the use of a computerized randomization/enrollment system that provided site personnel with patient numbers, package numbers, and randomization numbers."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation of patients to study groups proceeded through the use of a computerized randomization/enrollment system that provided site personnel with patient numbers, package numbers, and randomization numbers."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Each patient received his or her assigned treatment in individual blister packs that contained 2 tablets and 1 capsule per day. Columns A and B of the blister pack contained desvenlafaxine tablets or matching placebo and column C of the blister pack contained duloxetine capsules or matching placebo. The test article for each patient was packaged individually and code-labelled by Wyeth Research. Each patient package consisted of an 8-week supply of desvenlafaxine, duloxetine, or placebo plus 1 week of taper test article."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The modified ITT population was the primary population for efficacy analysis and included all patients who were randomly assigned to a study drug, had a baseline primary efficacy evaluation, were administered at least 1 dose of study medication, and had at least 1 primary efficacy evaluation after the first dose of double-blind test medication. The primary end point for all efficacy analyses was the last-observation-carried-forward (LOCF) final evaluation; the LOCF method was used to account for missing data"
Selective reporting (reporting bias)	Unclear risk	No SDs were reported for primary outcome. Response and remission rate were reported only as percentages
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Wade 2007

Methods	Multinational, multicentre, randomised, double-blind, parallel-group, fixed-dose, comparative study in outpatients with MDD. Eligible patients were randomised in a 1:1 ratio to double-blind treatment with fixed doses of either escitalopram (20mg) or duloxetine (60mg) for 24 weeks of treatment: patients randomised to escitalopram received 10mg/day for the first two weeks, and 20mg/day for the rest of the treatment period; patients randomised to duloxetine received 60mg/day for the whole treatment period All patients completing 24 weeks of treatment entered a 2-week double-blind taper period: patients randomised to escitalopram received 10mg/day in Weeks 25 and 26; patients randomised to duloxetine received 30mg/day in Weeks 25 and 26. In the week following the taper-down period (Week 27), patients received single-blind placebo
Participants	Outpatients with a primary diagnosis of MDD according to the DSM-IV-TR criteria, who had a MADRS total score ≥ 6 and a CGI-S score ≤ 4 at baseline and were between 18 and 65 years of age (extremes included) Country: Belgium, Canada, the Czech Republic, France, Germany, Italy, Spain, Sweden and the United Kingdom Setting: outpatients Age: patients aged between 18 and 65 years
Interventions	Duloxetine: 60 mg once daily Escitalopram: 20 mg once daily

Outcomes	<p>Primary efficacy variable: change from baseline to Week 24 in MADRS total score</p> <p>Secondary efficacy variables:</p> <ul style="list-style-type: none"> - change from baseline to each visit in MADRS total score - change from baseline to each visit in Hamilton Depression (HAM-D-17) - change from baseline to each visit in Hamilton Anxiety Scale (HAM-A) - change from Week 1 to each visit in CGI-I score - change from baseline to each visit in CGI-S score - proportion of responders (patients with a $\geq 50\%$ decrease from baseline in MADRS) - proportion of remitters (patients with a MADRS ≤ 12) <p>Safety: adverse events.</p>
Notes	<p>A safety follow-up visit was scheduled 4 weeks after the completion or withdrawal visit. All efficacy analyses are based on the FAS and LOCF</p> <p>First patient first visit - 23 September 2005</p> <p>Last patient last visit - 12 September 2006</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomized in a 1:1 ratio to double blind treatment with fixed doses of either escitalopram 20 mg/day or duloxetine 60 mg/day for 24 weeks of treatment according to a computer generated randomization list (...) at each study center sequentially enrolled patients were assigned the lowest randomization number available in blocks of four"
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomization series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Medication was supplied in wallet cards, identified by visit and patients were instructed to take one capsule a day to maintain double blinding during titration, treatment and taper periods (...) The medication was given as capsules of identical appearance, taste and smell (...) All study personnel and participants were blinded to treatment assignment for the duration of the entire study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analyses was conducted on an ITT basis.
Selective reporting (reporting bias)	Unclear risk	Only adverse events occurring with frequency $\geq 5\%$ are reported
Other bias	Unclear risk	Sponsorship bias cannot be ruled out.

Scales

AMDP-5: Association of Methodology of Documentation in Psychiatry-Module 5

ASEX: Arizona Sexual Experiences Scale

CG-I: Clinical Global Impression

CGI-S Clinical Global Impression - Severity scale

CSFQ: Chane in Sexual Functioning Questionnaire

DSM: Diagnostic and Statistical Manual

EQ-5D: European Quality of Life

GBR: Global Benefit Rating

HAM-A: Hamilton Anxiety Scale

HAM-D: Hamilton Depression Scale

HDRS: Hamilton Depression Rating Scale

ICD: International Classification of Diseases

IPT: interpersonal therapy

MADRS: Montgomery-Åsberg Depression Rating Scale

MINI: Mini International Neuropsychiatric Interview

PGI-I: Patient's Global Impressions of Improvement

PSQI: Pittsburgh Sleep Quality Index

SDS: Sheehan Disability Scale

SF-36: Short Form 36

VAS: visual analogues scale

Other

BID: twice daily

ITT: intention-to-treat~LOCF: last observation carried forward

MDD: major depressive disorder

QD: once daily

SD: standard deviation

SSRI: selective serotonin reuptake inhibitor

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Badyal 2006	Subgroup analysis of Patel 2011.
Herrera-Guzman 2009	Non-randomised design.
Higuchi 2009b	Wrong comparison (medium dose duloxetine vs low dose duloxetine)
ID#1126 (HMAI)	Duloxetine at sub-therapeutic doses (5, 10 and 20 mg/day).
Lam 2008	Pooled-analysis.
Lam 2010	Pooled-analysis.
Murasaki 2009a	Wrong intervention (sub-therapeutic dose of duloxetine).
Murasaki 2009b	Wrong intervention (sub-therapeutic dose of duloxetine).
NCT00666757	Wrong comparison.
NCT00810068	Wrong design and population.
Perahia 2008	Pooled-analysis.
Romera 2010	Wrong design and wrong population.
SCT-MD-39	The study recruited patients with initial non response to escitalopram (patients' selection bias). Note: study comparing escitalopram (20 mg/day) versus duloxetine (60 mg/day). Sponsored by Forest Laboratoires
Serafini 2010	Non-randomised design.
Tsutsui 2009	Wrong intervention (sub-therapeutic dose of duloxetine).

Characteristics of studies awaiting assessment [ordered by study ID]

Joubert 1997

Methods	Eight-week, double-blind, CCT.
Participants	Patients with major depression according to DSM-III-R. Absolute number of participants: 124.

Interventions	Clomipramine/ placebos/ duloxetine.
Outcomes	Not stated.
Notes	No full text available.

NCT00635219

Methods	Randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of three dosages of Lu AA21004, in acute treatment of major depressive disorder
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> Major Depressive Episode (MDE) as primary diagnosis according to DSM-IV-TR criteria (classification code 296.xx) Moderate to severe depression Current MDE duration of at least 3 months <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> Any current psychiatric disorder other than MDD as defined in the DSM-IV TR Any substance disorder within the previous 6 months Female patients of childbearing potential who are not using effective contraception Use of any psychoactive medication 2 weeks prior to screening and during the study <p>Other protocol-defined inclusion and exclusion criteria may apply</p>
Interventions	<p>Drug: Lu AA21004 Lu AA21004 2.5 mg/day</p> <p>Drug: Lu AA21004 Lu AA21004 5 mg/day</p> <p>Drug: Lu AA21004 Lu AA21004 10 mg/day</p> <p>Drug: Duloxetine Duloxetine 60 mg/day</p> <p>Drug: Placebo</p>
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> To evaluate the efficacy of three fixed dosages of Lu AA21004 versus placebo after 8 weeks of treatment in patients with MDD <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of Lu AA21004 compared to placebo during the course of treatment To evaluate the proportion of patients who respond to Lu AA21004 treatment at week 8 compared to placebo. Response is defined as a $\geq$ 50% decrease in Montgomery Åsberg Depression Rating Scale (MADRS) total score from baseline To evaluate the proportion of patients who are in remission after 8 weeks of treatment with Lu AA21004 as compared to placebo. Remission is defined as a MADRS total score $\leq$ 10 To evaluate the efficacy of Lu AA21004 compared to placebo after 1 week of treatment To evaluate the proportion of patients who are in sustained response after 1 week of treatment with Lu AA21004 compared to placebo. Sustained response is defined as a $\geq$ 50% decrease in MADRS total score from baseline obtained at week 1 and sustained throughout the treatment period To evaluate the effect of the Lu AA21004 on fatigue as assessed by the Fatigue Severity Scale (FSS) To evaluate the efficacy and safety of duloxetine versus placebo on the same parameters as mentioned for the Lu AA21004 To evaluate the effect of Lu AA21004 on health-related quality of life, disability and healthcare resource utilisation To evaluate the population pharmacokinetics of Lu AA21004 and its metabolites Lu AA34443 and Lu AA39835

- To evaluate the effect of Lu AA21004 on sexual function as assessed by Arizona Sexual Experiences Scale (ASEX)

Notes

NCT00672620

Methods	Randomised, double-blind, parallel-group, placebo-controlled, active-referenced, fixed-dose study comparing the efficacy and safety of 2 doses of Lu AA21004 in acute treatment of adults with major depressive disorder
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • The participant suffers from a major depressive episode as the primary diagnosis according to DSM of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria. • The reported duration of the current major depressive episode is at least 3 months. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • The participant has 1 or more the following: Any current psychiatric disorder other than major depressive disorder as defined in the DSM-IV-TR. Current or past history of: manic or hypomanic episode, schizophrenia, or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR. Any substance disorder (except nicotine and caffeine) within the previous 6 months as defined in the DSM-IV-TR. Presence or history of a clinically significant neurological disorder (including epilepsy). Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc). Any Axis II disorder that might compromise the study. • The participant has a significant risk of suicide according to the investigator's opinion or has a score ≥ 5 on item 10 (suicidal thoughts) of the Montgomery Åsberg Depression Rating Scale (MADRS) or has made a suicide attempt in the previous 6 months. • The current depressive symptoms of the participant are considered by the investigator to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each. • The participant has received electroconvulsive therapy within 6 months prior to Screening. • The participant is currently receiving formal cognitive or behavioral therapy, systematic psychotherapy, or plans to initiate such therapy during the study.
Interventions	<p>Drug: Lu AA21004 Lu AA21004 2.5 mg, capsules, orally, once daily for up to 8 weeks</p> <p>Drug: Lu AA21004 Lu AA21004 5 mg, capsules, orally, once daily for up to 8 weeks</p> <p>Drug: Duloxetine Duloxetine 60 mg, capsules, orally, once daily for up to 8 weeks</p> <p>Drug: Placebo</p>
Outcomes	<p>Primary Outcome Measures:</p> <p>The least squares mean change from baseline in the 24-item HDS total score after 8 weeks of treatment</p> <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> • The least squares mean change from baseline in the 24-item HDS total score at each week assessed. • Response rates at each week assessed, with response defined as a $\geq 50\%$ decrease in the 24-item HDS total score from baseline. • Sustained response from Week 1, with sustained response defined as a $\geq 20\%$ decrease from baseline in the 24-item HDS total score obtained at Week 1 and through week 6 and 50% decrease from baseline. • Remission rates at Week 8, with remission defined as a MADRS total score ≤ 10. • The least squares mean change from baseline in the MADRS total score • The least squares mean change from baseline in the CGI-Global Improvement Scale • The least squares mean change from baseline in the MADRS self-assessment. • Sheehan Disability Scale.

- Healthcare resource utilization as assessed by the Health Economic Assessment Questionnaire.
- The least squares mean change from baseline in the HAS
- The least squares mean change from baseline in the Clinical Global Impression Scale-Severity of Illness Scale

Notes

NCT00811252

Methods	Randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in acute treatment of major depressive disorder in elderly patients
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Participants	<p>Inclusion Criteria:</p> <p>Clinical Diagnosis of recurrent MDE according the DSM-IV-TR criteria with:</p> <ul style="list-style-type: none"> • Reported duration of the current episode of at least 4 weeks • MADRS total score ≥ 26 • At least one previous episode MDE before the age of 60 years <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Mini Mental State Exam (MMSE) < 24 • Any current anxiety disorder as defined in the DSM-IV-TR • Current or past history of manic or hypomanic episode, schizophrenia, or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR • Any substance disorder (except nicotine and caffeine) within the previous 6 months as defined in the DSMIV-TR • Presence or history of a clinically significant neurological disorder (including epilepsy) • Neurodegenerative disorder (Alzheimer's disease, Parkinson disease, multiple sclerosis, Huntington disease, etc) • Any Axis II disorder that might compromise the study • Significant risk of suicide according to the investigator's opinion, or has a score ≥ 5 on item 10 of the MADRS or has made a suicide attempt in the previous 6 months
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Interventions	<p>Drug: Lu AA21004 5 mg/day.</p> <p>Drug: Duloxetine 60 mg/day</p> <p>Drug: Placebo</p>
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Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> • Hamilton Depression Scale (HAM-D) <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> • Montgomery and Asberg Depression Rating Scale (MADRS), • Hamilton Anxiety Scale (HAM-A), • Clinical Global Impression: - Global Improvement (CGI-I) and - Severity of Illness (CGI-S), • Geriatric Depression Scale (GDS)
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Notes

NCT01145755

Methods	Phase IIa, multi-centre, randomised, double-blind, double-dummy, active and placebo-controlled, parallel group study to assess the effectiveness and safety of AZD2066 after 6 weeks of treatment in patients with major depressive disorder
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Provision of signed, written, and dated Informed Consent • Documented primary clinical diagnosis of MDD <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Patients with a secondary psychiatric disorder including bipolar disorder, psychotic disorders (i.e. schizophrenia, schizoaffective disorder, depression with psychotic features), GAD and social anxiety disorder • Patients whose current episode of depression started less than 4 weeks before enrolment • History of inadequate response of antidepressants during current depressive episode
Interventions	<p>Drug: AZD2066 18 mg once daily</p> <p>Drug: placebo</p> <p>Drug: duloxetine 60 mg once daily</p>
Outcomes	<p>Primary Outcome Measures:</p> <p>Change from baseline in MADRS total score to week 6 Time Frame: assessed on a once weekly basis for 6 weeks</p> <p>Secondary Outcome Measures:</p> <p>MADRS response defined as = 50% reduction in MADRS total score from baseline to Week 6 [Time Frame: assessed on a once weekly basis for 6 weeks;</p> <p>MADRS remission defined by MADRS total score of = 10 at Week 6 Time Frame: assessed on a once weekly basis for 6 weeks;</p> <p>Change in the HAM-D total score from baseline to Week 6.</p>
Notes	

ASEX: Arizona Sexual Experiences Scale

CCT: controlled clinical trial

CG-I: Clinical Global Impression

CGI-S Clinical Global Impression - Severity scale

DSM: Diagnostic and Statistical Manual

FFS: Fatigue Severity Scale

GAS: Global Assessment Scale

GDS: Geriatric Depression Scale

HAM-A: Hamilton Anxiety Scale

HAM-D: Hamilton Depression Scale

HDRS: Hamilton Depression Rating Scale

ICD: International Classification of Diseases

MADRS: Montgomery-Åsberg Depression Rating Scale

MDD: major depressive disorder

MDE: major depressive episode

MMSE: Mini-Mental State Examination

Characteristics of ongoing studies [ordered by study ID]

2008-004642-92

Trial name or title	Servier Laboratories Trial CL3-20098-062 [EudraCT Number: 2008-004642-92]
Methods	Evaluation of efficacy and clinical benefit of agomelatine (25 to 50 mg/day) over a 6-month treatment period in patients with major depressive disorder. A randomised, double-blind, international multicentre study with parallel groups versus duloxetine (60 mg/day). Twenty-four weeks of treatment
Participants	No information available
Interventions	Agomelatine 25 mg/day Agomelatine 50 mg/day Duloxetine 60 mg/day
Outcomes	No information available
Starting date	No information available
Contact information	[EudraCT Number: 2008-004642-92]. EU Clinical Trials Register [www.clinicaltrialsregister.eu/ctr-search/] 2009
Notes	

NCT01140906

Trial name or title	Efficacy and safety of Lu AA21004 in acute treatment of major depressive disorder
Methods	Randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study evaluating the efficacy and safety of Lu AA21004 (15 and 20 mg/Day) in the acute treatment of adult patients with major depressive disorder
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> The patient has recurrent MDD as the primary diagnosis according to DSM-IV-TR™ criteria (classification code 296.3x) The patient has a MADRS total score ≥ 26 The patient has a CGI-S score ≥ 4 <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> Any current anxiety psychiatric disorder as defined in the DSM-IV TR Current diagnosis or history of manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV TR Current diagnosis or history of alcohol or other substance abuse or dependence (excluding nicotine or caffeine) as defined in the DSM-IV TR Use of any psychoactive medication 2 weeks prior to screening and during the study The patient is at significant risk of suicide or has a score ≥ 5 on Item 10 (suicidal thoughts) of the MADRS, or has attempted suicide within 6 months prior to the Screening Visit <p>Other protocol-defined inclusion and exclusion criteria may apply</p>
Interventions	<p>Drug: Lu AA21004 15 mg/day.</p> <p>Drug: Lu AA21004 20 mg/day.</p> <p>Drug: Duloxetine 60 mg/day</p> <p>Drug: Placebo</p>
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> To evaluate the efficacy of two fixed doses of Lu AA21004 (15 or 20 mg/day) versus placebo as assessed by the change from baseline in MADRS total score after 8 weeks of treatment in adult patients with moderate to severe MDD. <p>Secondary Outcome Measures:</p>

- To compare the effect of Lu AA21004 to that of placebo at week 8 on patients who respond (response defined as a $\geq 50\%$ decrease in the MADRS total score from baseline)
- To compare the effect of Lu AA21004 to that of placebo at week 8 on global improvement as assessed by CGI-I
- To compare the effect of Lu AA21004 to that of placebo at week 8 on depressive symptoms in patients with a high baseline level of anxiety (defined by HAM-A), as assessed by MADRS total score
- To compare the effect of Lu AA21004 to that of placebo at week 8 on patients who are in remission (remission defined as a MADRS total score ≤ 10)
- To compare the effect of Lu AA21004 to that of placebo at week 8 on disability as assessed by SDS total score
- To evaluate the effect of Lu AA21004 on sexual function as assessed by ASEX versus placebo
- To evaluate the safety and tolerability of Lu AA21004 (15 or 20 mg/day) versus placebo during treatment
- To evaluate the potential discontinuation symptoms after abrupt discontinuation of treatment with Lu AA21004

Starting date	June 2010
Contact information	http://clinicaltrials.gov/ct2/show/NCT01140906
Notes	

NCT01153009

Trial name or title	Safety and efficacy of Lu AA21004 in adults with major depressive disorder
Methods	Phase 3, randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of 2 doses (15 and 20 mg) of Lu AA21004 in acute treatment of adults with major depressive disorder
Participants	<p>Inclusion Criteria:</p> <ol style="list-style-type: none"> 1 Man or a woman who suffers from a MDE recurrent as the primary diagnosis according to the DSM-IV-TR criteria (classification code 296.3x) as confirmed by the Structured Clinical Interview for DSM Disorders (SCID). 2 The reported duration of the current MDE is at least 3 months. 3 Has a MADRS total score of 26 or greater at Screening and baseline Visits. 4 Has a Clinical Global Impression - Severity of Illness (CGI-S) score of 4 or greater at Screening and baseline Visits. <p>Exclusion Criteria:</p> <ol style="list-style-type: none"> 1 Has previously participated in a Lu AA21004 clinical study. 2 Has 1 or more the following: Any current psychiatric disorder other than major depressive disorder (MDD) as defined in the DSM-IV-TR (as assessed by the SCID). Current or past history of: manic or hypomanic episode, schizophrenia or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorders, or mental disorders due to a general medical condition as defined in the DSM-IV-TR. Diagnosis of any substance abuse or dependence (except nicotine and caffeine) as defined in the DSM-IV-TR that has not been in sustained full remission for at least 2 years prior to screening (participant must also have negative urine drug screen prior to baseline). Presence or history of a clinically significant neurological disorder (including epilepsy). Neurodegenerative disorder (Alzheimer disease, Parkinson disease, multiple sclerosis, Huntington disease, etc). Any Axis II disorder that might compromise the study. 3 The current depressive symptoms are considered by the investigator to have been resistant to 2 adequate antidepressant treatments of at least 6 weeks duration each. Has 1 or more laboratory values outside the normal range, based on the blood or

urine samples taken at the Screening Visit, that are considered by the investigator to be clinically significant.

- 4 Has a thyroid stimulating hormone value outside the normal range at the Screening Visit that is deemed clinically significant by the investigator.
- 5 Has clinically significant abnormal vital signs as determined by the investigator.
- 6 Has an abnormal electrocardiogram as determined by the central reader and confirmed as clinically significant by the investigator.
- 7 Has an alanine aminotransferase, aspartate aminotransferase or total bilirubin level greater than 1.5 times the upper limits of normal.
- 8 Has a previous history of cancer that had been in remission for less than 5 years prior to the first dose of study medication. This criterion does not include those participants with basal cell or Stage I squamous cell carcinoma of the skin.
- 9 Has a disease or takes medication that, in the opinion of the investigator, could interfere with the assessments of safety, tolerability, or efficacy.
- 10 Has a known history of or currently has increased intraocular pressure or is at risk of acute narrow-angle glaucoma.
- 11 Has a clinically significant unstable illness, for example, hepatic impairment or renal insufficiency, or a cardiovascular, pulmonary, gastrointestinal, endocrine, neurological, rheumatologic, immunologic, infectious, skin and subcutaneous tissue disorders, or metabolic disturbance. The following are also considered unstable due to the potential impact on assessment of MDD response: pain disorder, chronic fatigue syndrome, fibromyalgia, and obstructive sleep apnoea.
- 12 Has a significant risk of suicide according to the investigator's opinion or has a score greater than or equal to 5 on item 10 (suicidal thoughts) of the MADRS or has made a suicide attempt in the previous 6 months.

Interventions	Drug: Lu AA21004 15 mg/day. Drug: Lu AA21004 20 mg/day. Drug: Duloxetine 60 mg/day Drug: Placebo
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> Change from baseline in the MADRS Total Score. <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> MADRS response at Week 8, with response defined as a 50% decrease in the MADRS total score from baseline. The change between MADRS score at week 8 or final visit and MADRS score at baseline. Mean Clinical Global Impression Scale - Improvement (CGI-I) score at Week 8. Change from baseline in MADRS total score at Week 8 in participants with baseline HAM-A total score ≥ 20. MADRS remission at Week 8, with remission defined as a MADRS total score ≤ 10. Change from baseline in Sheehan Disability Scale (SDS) total score at Week 8.
Starting date	June 2010
Contact information	http://clinicaltrials.gov/ct2/show/NCT01153009
Notes	

NCT01288079

Trial name or title	A study to assess the safety and effect of TC-5214 in patients with major depressive disorder
Methods	Phase IIb, randomised, double-blind, placebo-controlled, active controlled, parallel group, multicentre study to assess the safety and efficacy of 2 fixed-dose groups of TC-5214 (S-

mecamylamine) as monotherapy treatment in patients with major depressive disorder who exhibit an inadequate response to antidepressant therapy	
Participants	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> Provision of signed and dated informed consent before initiation of any study-related procedures. The patient must have a clinical diagnosis of major depressive disorder (MDD) with inadequate response to no more than one antidepressant. Women of child-bearing potential must have a negative urine pregnancy test and confirmed use of a highly effective form of birth control before enrolment and until 3 months after their last dose of study drug. Outpatient status at enrolment and randomisation. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> Patients with a lifetime history of bipolar disorder; psychotic disorder or post-traumatic stress disorder. Patients with a history of suicide attempts in the past year and/or seen by the investigator as having a significant history of risk of suicide or homicide. Patients with any significant unstable hepatic, renal, pulmonary, cardiovascular, ophthalmologic, neurologic, or any other medical conditions that might confound the study or put the patient at greater risk during study participation. History of stroke or transient ischaemic attack, seizures or seizure disorder, head trauma including closed head injury. Pregnancy or lactation.
Interventions	<p>Drug: TC-5214 2 mg/day (1 mg BID). Drug: TC-5214 8 mg/day (4 mg BID). Drug: Duloxetine 60 mg/day Drug: Placebo</p>
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> Change in the Montgomery Asberg Depression Rating Scale (MADRS) total score from randomisation (Week 8) to end of treatment (Week 16) <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> Changes in clinician rated symptoms as assessed by MADRS Changes in patient-reported outcomes as assessed by Sheehan Disability Scale (SDS) Adverse Events (AEs)(any incidence) and Serious Adverse Events (SAEs), will be assessed as a measure of safety and tolerability. Change in physical exam results, vital signs, lab tests (incl. ECG (electrocardiogram) will be assessed. Changes in clinician rated symptoms as assessed by Hamilton Rating Scale for Depression (HAM-D). Changes in clinician rated symptoms as assessed by Clinical Global Impression-Severity (CGI-S) Changes in clinician rated symptoms as assessed by Clinical Global Impression-Improvement (CGI-I) Changes in clinician rated symptoms as assessed by Hamilton Anxiety Assessment (HAM-A). Changes in patient-reported outcomes as assessed by European Quality of Life (EQ-5D). Changes in CSFQ (Changes Sexual Functioning Questionnaire) will be assessed. Changes in DESS (Discontinuation Emergent Signs and Symptoms) will be assessed. Changes in C-SSRS (Columbia Suicide Severity Rating Scale) will be assessed.
Starting date	February 2011

Contact information <http://www.clinicaltrials.gov/ct2/show/NCT01288079>

Notes

ASEX: Arizona Sexual Experiences Scale
 CG-I: Clinical Global Impression
 CGI-S Clinical Global Impression - Severity scale
 CSFQ: Sexual Functioning Questionnaire
 DESS: Discontinuation Emergent Signs and Symptoms
 C-SSRS: Columbia Suicide Severity Rating Scale
 DESS: Discontinuation Emergent Signs and Symptoms
 DSM: Diagnostic and Statistical Manual
 HAM-A: Hamilton Anxiety Scale
 HDRS: Hamilton Depression Rating Scale
 MDD: major depressive disorder
 MADRS: Montgomery-Åsberg Depression Rating Scale
 SDS: Sheehan Disability Scale

DATA AND ANALYSES

Comparison 1

Failure to respond at endpoint (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.87, 1.97]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.46, 1.44]
1.3 versus Paroxetine	6	1821	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.88, 1.43]
2 Duloxetine versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	474	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.56, 1.20]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.86, 1.88]
2.3 versus Venlafaxine	2	560	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.82, 1.68]

Comparison 2

Failure to respond (16-24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	295	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.79, 2.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.55]

Comparison 3

Failure to remit (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.62]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.17]
1.3 versus Paroxetine	6	1821	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.84, 1.25]
2 Duloxetine versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	474	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.49, 1.16]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.59, 1.40]
2.3 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.83, 1.53]

Comparison 4

Failure to remit (16-24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	295	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.86, 2.22]

Comparison 5

Mean difference at endpoint (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1096	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.09, 0.29]
1.2 versus Fluoxetine	2	219	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.41, 0.29]
1.3 versus Paroxetine	6	1387	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.16, 0.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Duloxetine versus newer ADs	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	2	648	Mean Difference (IV, Random, 95% CI)	0.60 [-0.46, 1.65]

Comparison 6

Mean difference (1-4 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	353	Mean Difference (IV, Random, 95% CI)	-0.51 [-1.41, 0.40]
2 Duloxetine versus newer ADs	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	2	608	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.94, 0.67]

Comparison 7

Standardised mean difference (16-24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	287	Mean Difference (IV, Random, 95% CI)	1.34 [-0.21, 2.89]

Comparison 8

Failure to complete (any cause)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.62 [1.01, 2.62]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.45, 1.46]
1.3 versus Paroxetine	6	1821	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.81, 1.30]
2 Duloxetine versus newer ADs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.62, 1.50]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.68, 1.60]
2.3 versus Venlafaxine	3	1051	Odds Ratio (M-H, Random, 95% CI)	1.56 [1.14, 2.15]

Comparison 9

Failure to complete (inefficacy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.24, 4.69]
1.2 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	0.29 [0.05, 1.85]
1.3 versus Paroxetine	5	1557	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.50, 1.83]
2 Duloxetine versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.21, 2.80]

Comparison 10

Failure to complete (side effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	2.31 [1.15, 4.65]
1.2 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	3.56 [0.42, 30.16]
1.3 versus Paroxetine	6	1821	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.80, 1.75]
2 Duloxetine versus newer ADs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	2.14 [1.11, 4.15]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.42, 1.28]
2.3 versus Venlafaxine	3	1051	Odds Ratio (M-H, Random, 95% CI)	1.93 [1.23, 3.01]

Comparison 11

SE - Participants with at least one TEAE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	11		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1112	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.75, 1.50]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.42, 2.54]
1.3 versus Paroxetine	6	1870	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.99, 1.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Duloxetine versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	1.53 [0.83, 2.80]
2.2 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.63, 2.74]

Comparison 12

SE - Abnormal thinking

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	1.85 [0.20, 17.11]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.18, 6.30]

Comparison 13

SE - Accidental injury

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.03, 7.30]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.37, 2.70]

Comparison 14

SE - Alanine aminotransferase increase

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	274	Odds Ratio (M-H, Random, 95% CI)	2.32 [0.11, 48.82]

Comparison 15

SE - Anorexia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.42, 6.02]
1.2 versus Paroxetine	4	1299	Odds Ratio (M-H, Random, 95% CI)	1.57 [0.95, 2.60]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	332	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.25]

Comparison 16

SE - Anxiety/agitation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	547	Odds Ratio (M-H, Random, 95% CI)	1.53 [0.61, 3.80]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.38, 2.53]
1.3 versus Paroxetine	4	1095	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.52, 2.88]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.71, 3.84]

Comparison 17

SE - Appetite decreased

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	547	Odds Ratio (M-H, Random, 95% CI)	1.76 [0.87, 3.57]
1.2 versus Paroxetine	2	752	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.50, 1.68]
2 Duloxetine versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	2.18 [1.25, 3.83]
2.2 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.22 [0.33, 4.47]

Comparison 18

SE - Appetite increased

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.24, 10.27]

Comparison 19

SE - Asthenia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.46, 1.92]
1.2 versus Paroxetine	3	1006	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.72, 2.21]

Comparison 20

SE - Chills

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.14, 13.60]

Comparison 21

SE - Constipation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	2	842	Odds Ratio (M-H, Random, 95% CI)	1.92 [0.92, 4.00]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.90 [0.20, 18.41]
1.3 versus Paroxetine	5	1573	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.85, 2.17]
2 Duloxetine versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	1.78 [0.90, 3.54]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.85, 3.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.60, 1.61]

Comparison 22

SE - Cough

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.14, 14.32]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.29, 2.31]

Comparison 23

SE - Diarrhoea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	295	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.40, 2.26]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.21, 2.33]
1.3 versus Paroxetine	5	1573	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.36, 1.46]
2 Duloxetine versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	3.20 [1.45, 7.09]
2.2 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.94, 2.43]

Comparison 24

SE - Dizziness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	2	842	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.97, 2.47]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.26, 6.30]
1.3 versus Paroxetine	5	1573	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.85, 1.72]
2 Duloxetine versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.68 [1.11, 2.55]

Comparison 25

SE - Dream activity increased

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.06, 3.23]
1.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	0.38 [0.10, 1.45]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	332	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.61, 4.82]

Comparison 26

SE - Dry mouth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.84 [1.29, 2.63]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.72, 2.85]
1.3 versus Paroxetine	5	1571	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.91, 1.82]
2 Duloxetine versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.66]
2.2 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.59, 1.22]

Comparison 27

SE - Dyspepsia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	295	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.12, 1.36]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.09, 9.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 versus Paroxetine	3	802	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.62, 3.57]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.26, 2.08]

Comparison 28

SE - Dyspnea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	274	Odds Ratio (M-H, Random, 95% CI)	2.32 [0.11, 48.82]

Comparison 29

SE - Fatigue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	2	842	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.62, 1.79]
1.2 versus Paroxetine	3	1045	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.68]
2 Duloxetine versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.74, 2.57]
2.2 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.76, 2.35]

Comparison 30

SE - Fever

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.02, 2.46]

Comparison 31**SE - Flatulence**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.06, 1.23]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.15, 1.20]

Comparison 32**SE - Headache**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.27]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.32, 1.24]
1.3 versus Paroxetine	5	1573	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.37]
2 Duloxetine versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	1.95 [1.12, 3.41]
2.2 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.69, 1.41]

Comparison 33**SE - Hypersomnia**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	538	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.08, 1.43]

Comparison 34**SE - Hypertonia**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.06, 3.23]

Comparison 35**SE - Hypertension**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.15, 5.29]
1.2 versus Paroxetine	1	274	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.06, 3.26]

Comparison 36**SE - Hypotonia**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	295	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.17, 1.57]

Comparison 37**SE - Infection**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.01, 52.30]

Comparison 38**SE - Influenza-like symptoms**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.14, 13.60]

Comparison 39**SE - Insomnia**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.88 [0.97, 3.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.44, 3.93]
1.3 versus Paroxetine	4	1095	Odds Ratio (M-H, Random, 95% CI)	1.62 [0.96, 2.73]
2 Duloxetine versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	1.60 [0.94, 2.72]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	12.99 [4.39, 38.46]
2.3 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.50, 1.83]

Comparison 40

SE - Musculoskeletal and connective tissue disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.26, 3.62]
1.2 versus Paroxetine	3	802	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.45, 2.81]

Comparison 41

SE - Nausea/vomiting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	1.82 [1.36, 2.44]
1.2 versus Fluoxetine	2	259	Odds Ratio (M-H, Random, 95% CI)	1.86 [0.89, 3.90]
1.3 versus Paroxetine	5	1573	Odds Ratio (M-H, Random, 95% CI)	1.46 [1.13, 1.89]
2 Duloxetine versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	1.53 [1.00, 2.37]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	6.63 [3.89, 11.31]
2.3 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.83, 3.32]

Comparison 42

SE - Nervousness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.85 [0.38, 9.04]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	1.77 [0.68, 4.61]

Comparison 43

SE - Pain (abdominal)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.08, 0.88]
1.2 versus Paroxetine	4	1095	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.59, 3.01]

Comparison 44

SE - Pain (back)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.11, 1.12]
1.2 versus Paroxetine	4	1095	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.51, 2.70]

Comparison 45

SE - Pain (chest)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.08, 10.77]
1.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.15, 3.06]

Comparison 46**SE - Pain (general)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.17, 1.60]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.36]

Comparison 47**SE - Pain (neck)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	7.70 [0.43, 136.35]

Comparison 48**SE - Palpitations**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.22, 6.12]
1.2 versus Paroxetine	4	1280	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.46, 2.92]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	332	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.12, 1.25]

Comparison 49**SE - Paraesthesia**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.12, 5.75]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	332	Odds Ratio (M-H, Random, 95% CI)	1.85 [0.61, 5.63]

Comparison 50**SE - Pharyngitis**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.29, 2.35]
1.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.07, 3.51]

Comparison 51**SE - Pruritus**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.08, 10.77]
1.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.12, 4.47]

Comparison 52**SE - Rash**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	2.39 [0.27, 20.81]
1.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	5.58 [0.31, 102.06]

Comparison 53**SE - Restlessness**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	274	Odds Ratio (M-H, Random, 95% CI)	0.15 [0.01, 3.75]

Comparison 54**SE - Rhinitis**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.49, 1.69]

Comparison 55**SE - Sexual problems**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Anorgasmia	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	538	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.46, 4.60]
2 Erectile dysfunction	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	5.63 [0.30, 104.82]
2.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.24, 4.03]
3 Loss of sexual interest	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 versus Escitalopram	1	547	Odds Ratio (M-H, Random, 95% CI)	1.29 [0.58, 2.90]
3.2 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.53]
3.3 versus Paroxetine	3	802	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.19, 2.79]
3.4 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	1.30 [0.60, 2.81]
4 Other sexual problems	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 versus Escitalopram	1	104	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.17, 1.94]
4.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.26, 2.51]
4.3 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.11, 4.37]

Comparison 56**SE - Sinusitis**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.03, 7.98]

Comparison 57

SE - Sleepiness/somnolence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.38, 1.19]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.45, 3.23]
1.3 versus Paroxetine	5	1571	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.66, 1.43]
2 Duloxetine versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	1.80 [0.99, 3.27]
2.2 versus Quetiapine	1	453	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.73]
2.3 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.52, 2.54]

Comparison 58

SE - Surgical procedure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	3.30 [0.17, 65.56]

Comparison 59

SE - Sweating

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	2	842	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.95, 3.07]
1.2 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.81 [0.78, 4.21]
1.3 versus Paroxetine	5	1573	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.78, 1.99]
2 Duloxetine versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.69, 1.59]

Comparison 60

SE - Tachycardia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	293	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.15, 14.54]

Comparison 61

SE - Tension

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	293	Odds Ratio (M-H, Random, 95% CI)	2.00 [0.22, 18.14]

Comparison 62

SE - Tinnitus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	538	Odds Ratio (M-H, Random, 95% CI)	1.79 [0.36, 8.84]

Comparison 63

SE - Tremor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.12, 9.92]
1.2 versus Paroxetine	4	1095	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.30, 1.56]
2 Duloxetine versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	2	823	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.61, 1.97]

Comparison 64**SE - Twitching**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	2.33 [0.11, 49.73]
1.2 versus Paroxetine	2	528	Odds Ratio (M-H, Random, 95% CI)	2.54 [0.55, 11.74]

Comparison 65**SE - Unespected benefit**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.20, 3.61]

Comparison 66**SE - Upper respiratory tract infection**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	2	842	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.44, 1.29]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.44, 2.50]

Comparison 67**SE - Urination problems**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.18, 3.31]
1.2 versus Paroxetine	2	557	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.29, 4.52]

Comparison 68**SE - Vasodilatation**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.24, 5.86]
1.2 versus Paroxetine	1	264	Odds Ratio (M-H, Random, 95% CI)	3.37 [0.74, 15.27]

Comparison 69**SE - Vertigo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	293	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.09, 11.05]

Comparison 70**SE - Visual problems (accommodation disorders, blurred vision, detached retina, mydriasis)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	2	222	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.24, 3.13]
1.2 versus Paroxetine	4	1299	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.55, 1.64]
2 Duloxetine versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Desvenlafaxine	1	455	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.27]
2.2 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.48, 2.29]

Comparison 71**SE - Weakness**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	1	274	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.06, 3.26]

Comparison 72**SE - Weight gain**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Paroxetine	2	567	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.28, 10.59]

Comparison 73**SE - Weight loss**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Fluoxetine	1	103	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.08, 10.77]
1.2 versus Paroxetine	2	567	Odds Ratio (M-H, Random, 95% CI)	2.73 [0.46, 16.26]

Comparison 74**SE - Yawning**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 versus Escitalopram	1	547	Odds Ratio (M-H, Random, 95% CI)	2.60 [0.99, 6.80]
1.2 versus Fluoxetine	1	119	Odds Ratio (M-H, Random, 95% CI)	4.30 [0.23, 81.94]
2 Duloxetine versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 versus Venlafaxine	1	491	Odds Ratio (M-H, Random, 95% CI)	4.22 [1.75, 10.17]

Comparison 75**Subgroup analysis - Failure to respond at endpoint (6-12 weeks)**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duloxetine versus paroxetine	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Duloxetine: less than 60 mg/day	3	568	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.66, 2.05]
1.2 Duloxetine: more than 60 but less than 90 mg/day	6	1407	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.87, 1.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Duloxetine: more than 90 mg/day	2	379	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.58, 1.38]

Analysis 1.1. Comparison 1 Failure to respond at endpoint (6-12 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 1 Failure to respond at endpoint (6-12 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 1.2. Comparison 1 Failure to respond at endpoint (6-12 weeks), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 1 Failure to respond at endpoint (6-12 weeks)

Outcome: 2 Duloxetine versus newer ADs

Analysis 2.1. Comparison 2 Failure to respond (16-24 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 2 Failure to respond (16-24 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 2.2. Comparison 2 Failure to respond (16-24 weeks), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 2 Failure to respond (16-24 weeks)

Outcome: 2 Duloxetine versus newer ADs

Analysis 3.1. Comparison 3 Failure to remit (6-12 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 3 Failure to remit (6-12 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 3.2. Comparison 3 Failure to remit (6-12 weeks), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 3 Failure to remit (6-12 weeks)

Outcome: 2 Duloxetine versus newer ADs

Analysis 4.1. Comparison 4 Failure to remit (16-24 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 4 Failure to remit (16-24 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 5.1. Comparison 5 Mean difference at endpoint (6-12 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 5 Mean difference at endpoint (6-12 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 5.2. Comparison 5 Mean difference at endpoint (6-12 weeks), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 5 Mean difference at endpoint (6-12 weeks)

Outcome: 2 Duloxetine versus newer ADs

Analysis 6.1. Comparison 6 Mean difference (1-4 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 6 Mean difference (1-4 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 6.2. Comparison 6 Mean difference (1-4 weeks), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 6 Mean difference (1-4 weeks)

Outcome: 2 Duloxetine versus newer ADs

Analysis 7.1. Comparison 7 Standardised mean difference (16-24 weeks), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 7 Standardised mean difference (16-24 weeks)

Outcome: 1 Duloxetine versus SSRIs

Analysis 8.1. Comparison 8 Failure to complete (any cause), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 8 Failure to complete (any cause)

Outcome: 1 Duloxetine versus SSRIs

Analysis 8.2. Comparison 8 Failure to complete (any cause), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 8 Failure to complete (any cause)

Outcome: 2 Duloxetine versus newer ADs

Analysis 9.1. Comparison 9 Failure to complete (inefficacy), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 9 Failure to complete (inefficacy)

Outcome: 1 Duloxetine versus SSRIs

Analysis 9.2. Comparison 9 Failure to complete (inefficacy), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 9 Failure to complete (inefficacy)

Outcome: 2 Duloxetine versus newer ADs

Analysis 10.1. Comparison 10 Failure to complete (side effects), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 10 Failure to complete (side effects)

Outcome: 1 Duloxetine versus SSRIs

Analysis 10.2. Comparison 10 Failure to complete (side effects), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 10 Failure to complete (side effects)

Outcome: 2 Duloxetine versus newer ADs

Analysis 11.1. Comparison 11 SE - Participants with at least one TEAE, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 11 SE - Participants with at least one TEAE

Outcome: 1 Duloxetine versus SSRIs

Analysis 11.2. Comparison 11 SE - Participants with at least one TEAE, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 11 SE - Participants with at least one TEAE

Outcome: 2 Duloxetine versus newer ADs

Analysis 12.1. Comparison 12 SE - Abnormal thinking, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 12 SE - Abnormal thinking

Outcome: 1 Duloxetine versus SSRIs

Analysis 13.1. Comparison 13 SE - Accidental injury, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 13 SE - Accidental injury

Outcome: 1 Duloxetine versus SSRIs

Analysis 14.1. Comparison 14 SE - Alanine aminotransferase increase, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 14 SE - Alanine aminotransferase increase

Outcome: 1 Duloxetine versus SSRIs

Analysis 15.1. Comparison 15 SE - Anorexia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 15 SE - Anorexia

Outcome: 1 Duloxetine versus SSRIs

Analysis 15.2. Comparison 15 SE - Anorexia, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 15 SE - Anorexia

Outcome: 2 Duloxetine versus newer ADs

Analysis 16.1. Comparison 16 SE - Anxiety/agitation, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 16 SE - Anxiety/agitation

Outcome: 1 Duloxetine versus SSRIs

Analysis 16.2. Comparison 16 SE - Anxiety/agitation, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 16 SE - Anxiety/agitation

Outcome: 2 Duloxetine versus newer ADs

Analysis 17.1. Comparison 17 SE - Appetite decreased, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 17 SE - Appetite decreased

Outcome: 1 Duloxetine versus SSRIs

Analysis 17.2. Comparison 17 SE - Appetite decreased, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 17 SE - Appetite decreased

Outcome: 2 Duloxetine versus newer ADs

Analysis 18.1. Comparison 18 SE - Appetite increased, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 18 SE - Appetite increased

Outcome: 1 Duloxetine versus SSRIs

Analysis 19.1. Comparison 19 SE - Asthenia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 19 SE - Asthenia

Outcome: 1 Duloxetine versus SSRIs

Analysis 20.1. Comparison 20 SE - Chills, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 20 SE - Chills

Outcome: 1 Duloxetine versus SSRIs

Analysis 21.1. Comparison 21 SE - Constipation, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 21 SE - Constipation

Outcome: 1 Duloxetine versus SSRIs

Analysis 21.2. Comparison 21 SE - Constipation, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 21 SE - Constipation

Outcome: 2 Duloxetine versus newer ADs

Analysis 22.1. Comparison 22 SE - Cough, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 22 SE - Cough

Outcome: 1 Duloxetine versus SSRIs

Analysis 23.1. Comparison 23 SE - Diarrhoea, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 23 SE - Diarrhoea

Outcome: 1 Duloxetine versus SSRIs

Analysis 23.2. Comparison 23 SE - Diarrhoea, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 23 SE - Diarrhoea

Outcome: 2 Duloxetine versus newer ADs

Analysis 24.1. Comparison 24 SE - Dizziness, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 24 SE - Dizziness

Outcome: 1 Duloxetine versus SSRIs

Analysis 24.2. Comparison 24 SE - Dizziness, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 24 SE - Dizziness

Outcome: 2 Duloxetine versus newer ADs

Analysis 25.1. Comparison 25 SE - Dream activity increased, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 25 SE - Dream activity increased

Outcome: 1 Duloxetine versus SSRIs

Analysis 25.2. Comparison 25 SE - Dream activity increased, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 25 SE - Dream activity increased

Outcome: 2 Duloxetine versus newer ADs

Analysis 26.1. Comparison 26 SE - Dry mouth, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 26 SE - Dry mouth

Outcome: 1 Duloxetine versus SSRIs

Analysis 26.2. Comparison 26 SE - Dry mouth, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 26 SE - Dry mouth

Outcome: 2 Duloxetine versus newer ADs

Analysis 27.1. Comparison 27 SE - Dyspepsia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 27 SE - Dyspepsia

Outcome: 1 Duloxetine versus SSRIs

Analysis 27.2. Comparison 27 SE - Dyspepsia, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 27 SE - Dyspepsia

Outcome: 2 Duloxetine versus newer ADs

Analysis 28.1. Comparison 28 SE - Dyspnea, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 28 SE - Dyspnea

Outcome: 1 Duloxetine versus SSRIs

Analysis 29.1. Comparison 29 SE - Fatigue, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 29 SE - Fatigue

Outcome: 1 Duloxetine versus SSRIs

Analysis 29.2. Comparison 29 SE - Fatigue, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 29 SE - Fatigue

Outcome: 2 Duloxetine versus newer ADs

Analysis 30.1. Comparison 30 SE - Fever, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 30 SE - Fever

Outcome: 1 Duloxetine versus SSRIs

Analysis 31.1. Comparison 31 SE - Flatulence, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 31 SE - Flatulence

Outcome: 1 Duloxetine versus SSRIs

Analysis 32.1. Comparison 32 SE - Headache, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 32 SE - Headache

Outcome: 1 Duloxetine versus SSRIs

Analysis 32.2. Comparison 32 SE - Headache, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 32 SE - Headache

Outcome: 2 Duloxetine versus newer ADs

Analysis 33.1. Comparison 33 SE - Hypersomnia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 33 SE - Hypersomnia

Outcome: 1 Duloxetine versus SSRIs

Analysis 34.1. Comparison 34 SE - Hypertonia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 34 SE - Hypertonia

Outcome: 1 Duloxetine versus SSRIs

Analysis 35.1. Comparison 35 SE - Hypertension, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 35 SE - Hypertension

Outcome: 1 Duloxetine versus SSRIs

Analysis 36.1. Comparison 36 SE - Hypotonia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 36 SE - Hypotonia

Outcome: 1 Duloxetine versus SSRIs

Analysis 37.1. Comparison 37 SE - Infection, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 37 SE - Infection

Outcome: 1 Duloxetine versus SSRIs

Analysis 38.1. Comparison 38 SE - Influenza-like symptoms, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 38 SE - Influenza-like symptoms

Outcome: 1 Duloxetine versus SSRIs

Analysis 39.1. Comparison 39 SE - Insomnia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 39 SE - Insomnia

Outcome: 1 Duloxetine versus SSRIs

Analysis 39.2. Comparison 39 SE - Insomnia, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 39 SE - Insomnia

Outcome: 2 Duloxetine versus newer ADs

Analysis 40.1. Comparison 40 SE - Musculoskeletal and connective tissue disorders, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 40 SE - Musculoskeletal and connective tissue disorders

Outcome: 1 Duloxetine versus SSRIs

Analysis 41.1. Comparison 41 SE - Nausea/vomiting, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 41 SE - Nausea/vomiting

Outcome: 1 Duloxetine versus SSRIs

Analysis 41.2. Comparison 41 SE - Nausea/vomiting, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 41 SE - Nausea/vomiting

Outcome: 2 Duloxetine versus newer ADs

Analysis 42.1. Comparison 42 SE - Nervousness, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 42 SE - Nervousness

Outcome: 1 Duloxetine versus SSRIs

Analysis 43.1. Comparison 43 SE - Pain (abdominal), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 43 SE - Pain (abdominal)

Outcome: 1 Duloxetine versus SSRIs

Analysis 44.1. Comparison 44 SE - Pain (back), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 44 SE - Pain (back)

Outcome: 1 Duloxetine versus SSRIs

Analysis 45.1. Comparison 45 SE - Pain (chest), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 45 SE - Pain (chest)

Outcome: 1 Duloxetine versus SSRIs

Analysis 46.1. Comparison 46 SE - Pain (general), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 46 SE - Pain (general)

Outcome: 1 Duloxetine versus SSRIs

Analysis 47.1. Comparison 47 SE - Pain (neck), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 47 SE - Pain (neck)

Outcome: 1 Duloxetine versus SSRIs

Analysis 48.1. Comparison 48 SE - Palpitations, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 48 SE - Palpitations

Outcome: 1 Duloxetine versus SSRIs

Analysis 48.2. Comparison 48 SE - Palpitations, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 48 SE - Palpitations

Outcome: 2 Duloxetine versus newer ADs

Analysis 49.1. Comparison 49 SE - Paraesthesia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 49 SE - Paraesthesia

Outcome: 1 Duloxetine versus SSRIs

Analysis 49.2. Comparison 49 SE - Paraesthesia, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 49 SE - Paraesthesia

Outcome: 2 Duloxetine versus newer ADs

Analysis 50.1. Comparison 50 SE - Pharyngitis, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 50 SE - Pharyngitis

Outcome: 1 Duloxetine versus SSRIs

Analysis 51.1. Comparison 51 SE - Pruritus, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 51 SE - Pruritus

Outcome: 1 Duloxetine versus SSRIs

Analysis 52.1. Comparison 52 SE - Rash, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 52 SE - Rash

Outcome: 1 Duloxetine versus SSRIs

Analysis 53.1. Comparison 53 SE - Restlessness, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 53 SE - Restlessness

Outcome: 1 Duloxetine versus SSRIs

Analysis 54.1. Comparison 54 SE - Rhinitis, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 54 SE - Rhinitis

Outcome: 1 Duloxetine versus SSRIs

Analysis 55.1. Comparison 55 SE - Sexual problems, Outcome 1 Anorgasmia

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 55 SE - Sexual problems

Outcome: 1 Anorgasmia

Analysis 55.2. Comparison 55 SE - Sexual problems, Outcome 2 Erectile dysfunction

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 55 SE - Sexual problems

Outcome: 2 Erectile dysfunction

Analysis 55.3. Comparison 55 SE - Sexual problems, Outcome 3 Loss of sexual interest

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 55 SE - Sexual problems

Outcome: 3 Loss of sexual interest

Analysis 55.4. Comparison 55 SE - Sexual problems, Outcome 4 Other sexual problems

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 55 SE - Sexual problems

Outcome: 4 Other sexual problems

Analysis 56.1. Comparison 56 SE - Sinusitis, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 56 SE - Sinusitis

Outcome: 1 Duloxetine versus SSRIs

Analysis 57.1. Comparison 57 SE - Sleepiness/somnolence, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 57 SE - Sleepiness/somnolence

Outcome: 1 Duloxetine versus SSRIs

Analysis 57.2. Comparison 57 SE - Sleepiness/somnolence, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 57 SE - Sleepiness/somnolence

Outcome: 2 Duloxetine versus newer ADs

Analysis 58.1. Comparison 58 SE - Surgical procedure, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 58 SE - Surgical procedure

Outcome: 1 Duloxetine versus SSRIs

Analysis 59.1. Comparison 59 SE - Sweating, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 59 SE - Sweating

Outcome: 1 Duloxetine versus SSRIs

Analysis 59.2. Comparison 59 SE - Sweating, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 59 SE - Sweating

Outcome: 2 Duloxetine versus newer ADs

Analysis 60.1. Comparison 60 SE - Tachycardia, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 60 SE - Tachycardia

Outcome: 1 Duloxetine versus SSRIs

Analysis 61.1. Comparison 61 SE - Tension, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 61 SE - Tension

Outcome: 1 Duloxetine versus SSRIs

Analysis 62.1. Comparison 62 SE - Tinnitus, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 62 SE - Tinnitus

Outcome: 1 Duloxetine versus SSRIs

Analysis 63.1. Comparison 63 SE - Tremor, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 63 SE - Tremor

Outcome: 1 Duloxetine versus SSRIs

Analysis 63.2. Comparison 63 SE - Tremor, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 63 SE - Tremor

Outcome: 2 Duloxetine versus newer ADs

Analysis 64.1. Comparison 64 SE - Twitching, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 64 SE - Twitching

Outcome: 1 Duloxetine versus SSRIs

Analysis 65.1. Comparison 65 SE - Unespected benefit, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 65 SE - Unespected benefit

Outcome: 1 Duloxetine versus SSRIs

Analysis 66.1. Comparison 66 SE - Upper respiratory tract infection, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 66 SE - Upper respiratory tract infection

Outcome: 1 Duloxetine versus SSRIs

Analysis 66.2. Comparison 66 SE - Upper respiratory tract infection, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 66 SE - Upper respiratory tract infection

Outcome: 2 Duloxetine versus newer ADs

Analysis 67.1. Comparison 67 SE - Urination problems, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 67 SE - Urination problems

Outcome: 1 Duloxetine versus SSRIs

Analysis 68.1. Comparison 68 SE - Vasodilatation, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 68 SE - Vasodilatation

Outcome: 1 Duloxetine versus SSRIs

Analysis 69.1. Comparison 69 SE - Vertigo, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 69 SE - Vertigo

Outcome: 1 Duloxetine versus SSRIs

Analysis 70.1. Comparison 70 SE - Visual problems (accommodation disorders, blurred vision, detached retina, mydriasis), Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 70 SE - Visual problems (accommodation disorders, blurred vision, detached retina, mydriasis)

Outcome: 1 Duloxetine versus SSRIs

Analysis 70.2. Comparison 70 SE - Visual problems (accommodation disorders, blurred vision, detached retina, mydriasis), Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 70 SE - Visual problems (accommodation disorders, blurred vision, detached retina, mydriasis)

Outcome: 2 Duloxetine versus newer ADs

Analysis 71.1. Comparison 71 SE - Weakness, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 71 SE - Weakness

Outcome: 1 Duloxetine versus SSRIs

Analysis 72.1. Comparison 72 SE - Weight gain, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 72 SE - Weight gain

Outcome: 1 Duloxetine versus SSRIs

Analysis 73.1. Comparison 73 SE - Weight loss, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 73 SE - Weight loss

Outcome: 1 Duloxetine versus SSRIs

Analysis 74.1. Comparison 74 SE - Yawning, Outcome 1 Duloxetine versus SSRIs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 74 SE - Yawning

Outcome: 1 Duloxetine versus SSRIs

Analysis 74.2. Comparison 74 SE - Yawning, Outcome 2 Duloxetine versus newer ADs

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 74 SE - Yawning

Outcome: 2 Duloxetine versus newer ADs

Analysis 75.1. Comparison 75 Subgroup analysis - Failure to respond at endpoint (6-12 weeks), Outcome 1 Duloxetine versus paroxetine

Review: Duloxetine versus other anti-depressive agents for depression

Comparison: 75 Subgroup analysis - Failure to respond at endpoint (6-12 weeks)

Outcome: 1 Duloxetine versus paroxetine

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the analyses, the cut-off point for remission was set at 12 or less on the MADRS (instead of 10), because all studies included in the present review used this cut-off point for defining remission.

We slightly changed the inclusion criteria for “types of intervention” to include trials investigating duloxetine versus quetiapine, as follows: “Trials in which duloxetine was compared to another type of psychopharmacological agent (i.e., anxiolytics, anticonvulsants or mood-stabilisers) were excluded.” The previous version of the text was as follows: “Trials in which duloxetine was compared to another type of psychopharmacological agent (i.e., anxiolytics, anticonvulsants, antipsychotics or mood-stabilisers) were excluded.” Our decision was based on clinical grounds, to be as informative as possible, as quetiapine is frequently used for depressive symptoms, not only in bipolar disorder (see text of the review for more details).

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 10, 2012

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Duloxetine versus other antidepressive agents for depression

Although pharmacological and psychological interventions are both effective for major depression, antidepressant drugs remain the mainstay of treatment in moderate to severe major depression. During the last 20 years, newer compounds (such as selective serotonin reuptake inhibitors and dual action agents such as serotonin noradrenalin reuptake inhibitors) have progressively become the most commonly prescribed antidepressants. Duloxetine hydrochloride, one of the most recent antidepressants introduced in the market, is a selective serotonin noradrenergic reuptake inhibitor for oral administration. In the present review we assessed the evidence for the efficacy, acceptability and tolerability of duloxetine in comparison with all other antidepressants in the acute-phase treatment of major depression. Sixteen randomised controlled trials (5735 participants) were included. Duloxetine was not more effective than some other new antidepressant agents in the acute-phase treatment of major depression, and it was less well tolerated than escitalopram and venlafaxine as more patients allocated to duloxetine withdrew treatment before study end. However, due to the limited number of studies per comparison these results should be interpreted with caution.

Figure 1.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cutler 2009	+	?	+	+	?	?
Detke 2004 (HMA Y A)	+	?	?	+	?	?
Goldstein 2002 (HMA Q A)	+	?	?	+	?	?
Goldstein 2004 (HMA T B)	+	?	?	+	?	?
Higuchi 2009a	+	+	+	+	?	+
ID#3327 (HMA Q B)	+	?	?	?	?	?
ID#4091 (HMA T A)	+	?	?	?	?	?
ID#7999 (HMA C Q)	+	?	?	?	?	?
Khan 2007 (SCT-MD-23)	+	?	?	+	?	?
Lee 2007 (HMA C V)	+	?	?	+	?	?
Nierenberg 2007 (HMA C R)	+	?	?	?	?	?
Patel 2011	+	?	?	-	-	?
Perahia 2006 (HMA Y B)	+	?	?	?	?	?
Perahia 2008 (HMA B U)	+	?	?	?	?	?
Tourian 2009	+	+	+	+	?	?
Wade 2007	+	+	+	?	?	?

Figure 2.

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

Figure 3.

Forest plot of comparison: 1 Failure to respond at endpoint (6-12 weeks), outcome: 1.2
Duloxetine versus other SSRIs.

Figure 4.

Forest plot of comparison: 8 Failure to complete (any cause), outcome: 8.2 Duloxetine versus other SSRIs.

Figure 5.

Forest plot of comparison: 8 Failure to complete (any cause), outcome: 8.2 Duloxetine versus newer ADs.

Table 1

Adverse events

Adverse event	Study	Duloxetine		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Duloxetine versus SSRIs						
Duloxetine vs escitalopram						
Appetite decreased	Nierenberg 2007 (HMCR)	22	273	13	274	1.76 [0.87, 3.57]
Dizziness	Nierenberg 2007 (HMCR); Wade 2007	50	424	33	418	1.55 [0.97, 2.47]
Dyspepsia	Wade 2007	4	151	9	144	0.41 [0.12, 1.36]
Fatigue	Nierenberg 2007 (HMCR); Wade 2007	31	424	29	418	1.05 [0.62, 1.79]
Headache	Khan 2007 (SCT-MD-23); Nierenberg 2007 (HMCR); Wade 2007	98	562	104	558	0.92 [0.66, 1.27]
Hypotonia	Wade 2007	5	151	9	144	0.51 [0.17, 1.57]
Sexual problems (loss of sexual interest)	Nierenberg 2007 (HMCR)	14	273	11	274	1.29 [0.58, 2.90]
Sweating	Nierenberg 2007 (HMCR); Wade 2007	32	424	19	418	1.71 [0.95, 3.07]
Upper respiratory tract infection	Nierenberg 2007 (HMCR); Wade 2007	26	424	33	418	0.76 [0.44, 1.29]
Yawning	Nierenberg 2007 (HMCR)	15	273	6	274	2.60 [0.99, 6.80]
Duloxetine vs fluoxetine						
Abnormal thinking	ID#3327 (HMAQ B)	4	82	1	37	1.85 [0.20, 17.11]
Accidental injury	ID#3327 (HMAQ B)	1	82	1	37	0.44 [0.03, 7.30]
Anorexia	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	10	152	3	70	1.59 [0.42, 6.02]
Appetite increased	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	5	152	1	70	1.55 [0.24, 10.27]
Asthenia	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	29	152	14	70	0.94 [0.46, 1.92]
Chills	ID#3327 (HMAQ B)	3	82	1	37	1.37 [0.14, 13.60]
Cough	Goldstein 2002 (HMAQ A)	3	70	1	33	1.43 [0.14, 14.32]
Dizziness	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	15	152	5	70	1.29 [0.26, 6.30]
Dream activity increased	ID#3327 (HMAQ B)	2	82	2	37	0.44 [0.06, 3.23]
Dyspepsia	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	11	152	6	70	0.93 [0.09, 9.03]
Fever	ID#3327 (HMAQ B)	1	82	2	37	0.22 [0.02, 2.46]
Flatulence	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	3	152	5	70	0.27 [0.06, 1.23]
Headache	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	29	152	19	70	0.63 [0.32, 1.24]
Hypertonia	ID#3327 (HMAQ B)	2	82	2	37	0.44 [0.06, 3.23]
Hypertension	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	4	152	2	70	0.89 [0.15, 5.29]

Adverse event	Study	Duloxetine		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Infection	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	6	152	2	70	0.78 [0.01, 52.30]
Influenza-like symptoms	ID#3327 (HMAQ B)	3	82	1	37	1.37 [0.14, 13.60]
Musculoskeletal and connective tissue disorders	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	7	152	3	70	0.97 [0.26, 3.62]
Nervousness	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	8	152	2	70	1.85 [0.38, 9.04]
Pain (back)	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	6	152	7	70	0.35 [0.11, 1.12]
Pain (chest)	Goldstein 2002 (HMAQ A)	2	70	1	33	0.94 [0.08, 10.77]
Pain (general)	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	7	152	6	70	0.52 [0.17, 1.60]
Palpitations	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	5	152	2	70	1.15 [0.22, 6.12]
Pharyngitis	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	11	152	6	70	0.83 [0.29, 2.35]
Pruritus	Goldstein 2002 (HMAQ A)	2	70	1	33	0.94 [0.08, 10.77]
Rash	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	4	152	0	70	2.39 [0.27, 20.81]
Sexual problems (erectile dysfunction)	Goldstein 2002 (HMAQ A)	5	70	0	33	5.63 [0.30, 104.82]
Sexual problems (loss of sexual interest)	ID#3327 (HMAQ B)	5	82	5	37	0.42 [0.11, 1.53]
Sexual problems (others)	Goldstein 2002 (HMAQ A)	3	70	2	33	0.69 [0.11, 4.37]
Sinusitis	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	3	152	3	70	0.49 [0.03, 7.98]
Surgical procedure	ID#3327 (HMAQ B)	3	82	0	37	3.30 [0.17, 65.56]
Sweating	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	29	152	8	70	1.81 [0.78, 4.21]
Tremor	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	6	152	2	70	1.09 [0.12, 9.92]
Twitching	ID#3327 (HMAQ B)	2	82	0	37	2.33 [0.11, 49.73]
Vasodilatation	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	9	152	3	70	1.18 [0.24, 5.86]
Visual problems	Goldstein 2002 (HMAQ A); ID#3327 (HMAQ B)	8	152	4	70	0.87 [0.24, 3.13]
Weight loss	Goldstein 2002 (HMAQ A)	2	70	1	33	0.94 [0.08, 10.77]
Yawning	ID#3327 (HMAQ B)	4	82	0	37	4.30 [0.23, 81.94]
<i>Duloxetine vs paroxetine</i>						
Abnormal thinking	Goldstein 2004 (HMAQ B); ID#4091 (HMAQ A)	9	352	4	176	1.07 [0.18, 6.30]
Accidental injury	Goldstein 2004 (HMAQ B); ID#4091 (HMAQ A)	12	352	6	176	0.99 [0.37, 2.70]
Alanine amino-transferase increase	Detke 2004 (HMAQ A)	2	188	0	86	2.32 [0.11, 48.82]
Anorexia	Goldstein 2004 (HMAQ B); ID#4091 (HMAQ A); Lee 2007 (HMAQ B); Perahia 2006 (HMAQ B)	58	786	26	513	1.57 [0.95, 2.60]

Adverse event	Study	Duloxetine		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Appetite decreased	Detke 2004 (HMAY A); Lee 2007 (HMCV)	23	426	22	326	0.91 [0.50, 1.68]
Asthenia	Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Lee 2007 (HMCV)	48	590	24	416	1.26 [0.72, 2.21]
Cough	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	10	352	6	176	0.82 [0.29, 2.31]
Dizziness	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Lee 2007 (HMCV); Perahia 2006 (HMAY B)	95	974	62	599	1.21 [0.85, 1.72]
Dream activity increased	Goldstein 2004 (HMAT B)	4	177	5	87	0.38 [0.10, 1.45]
Dyspepsia	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	21	540	7	262	1.49 [0.62, 3.57]
Dyspnea	Detke 2004 (HMAY A)	2	188	0	86	2.32 [0.11, 48.82]
Fatigue	Detke 2004 (HMAY A); Lee 2007 (HMCV); Perahia 2006 (HMAY B)	17	622	17	423	0.84 [0.42, 1.68]
Flatulence	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	7	352	8	176	0.43 [0.15, 1.20]
Headache	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Lee 2007 (HMCV); Perahia 2006 (HMAY B)	118	972	73	599	0.99 [0.72, 1.37]
Hypersomnia	Detke 2004 (HMAY A); ID#4091 (HMAT A)	3	363	5	175	0.34 [0.08, 1.43]
Hypertension	Detke 2004 (HMAY A)	2	188	2	86	0.45 [0.06, 3.26]
Musculoskeletal and connective tissue disorders	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	16	540	7	262	1.13 [0.45, 2.81]
Nervousness	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	25	352	7	176	1.77 [0.68, 4.61]
Pain	(abdominal) Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Perahia 2006 (HMAY B)	23	736	8	359	1.34 [0.59, 3.01]
Pain (back)	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Perahia 2006 (HMAY B)	22	736	8	359	1.17 [0.51, 2.70]
Pain (chest)	ID#4091 (HMAT A)	4	175	3	89	0.67 [0.15, 3.06]
Pain (general)	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	21	352	15	176	0.68 [0.34, 1.36]
Pain (neck)	Goldstein 2004 (HMAT B)	7	177	0	87	7.70 [0.43, 136.35]
Palpitations	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Lee 2007 (HMCV)	33	778	18	502	1.16 [0.46, 2.92]
Paraesthesia	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	8	352	5	176	0.83 [0.12, 5.75]
Pharyngitis	Goldstein 2004 (HMAT B)	2	177	2	87	0.49 [0.07, 3.51]
Pruritus	Goldstein 2004 (HMAT B)	3	177	2	87	0.73 [0.12, 4.47]
Rash	Goldstein 2004 (HMAT B)	5	177	0	87	5.58 [0.31, 102.06]
Restlessness	Detke 2004 (HMAY A)	0	188	1	86	0.15 [0.01, 3.75]

Adverse event	Study	Duloxetine		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Rhinitis	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	31	352	17	176	0.91 [0.49, 1.69]
Sexual problems (anorgasmia)	Detke 2004 (HMAY A); Goldstein 2004 (HMATB)	12	365	4	173	1.45 [0.46, 4.60]
Sexual problems (erectile dysfunction)	Goldstein 2004 (HMAT B)	6	177	3	87	0.98 [0.24, 4.03]
Sexual problems (loss of sexual interest)	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	20	540	12	262	0.74 [0.19, 2.79]
Sexual problems (others)	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	10	352	6	176	0.80 [0.26, 2.51]
Sweating	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Lee 2007 (HMCV); Perahia 2006 (HMAY B)	60	974	29	599	1.25 [0.78, 1.99]
Tachycardia	Perahia 2006 (HMAY B)	3	196	1	97	1.49 [0.15, 14.54]
Tension	Perahia 2006 (HMAY B)	4	196	1	97	2.00 [0.22, 18.14]
Tinnitus	Detke 2004 (HMAY A); Goldstein 2004 (HMATB)	8	365	2	173	1.79 [0.36, 8.84]
Tremor	Detke 2004 (HMAY A); Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Perahia 2006 (HMAY B)	16	736	11	359	0.69 [0.30, 1.56]
Twitching	Goldstein 2004 (HMAT B); ID#4091 (HMAT A)	10	352	2	176	2.54 [0.55, 11.74]
Unexpected benefit	ID#4091 (HMAT A)	5	175	3	89	0.84 [0.20, 3.61]
Vasodilatation	Goldstein 2004 (HMAT B)	13	177	2	87	3.37 [0.74, 15.27]
Vertigo	Perahia 2006 (HMAY B)	2	196	1	97	0.99 [0.09, 11.05]
Visual problems	Goldstein 2004 (HMAT B); ID#4091 (HMAT A); Lee 2007 (HMCV); Perahia 2006 (HMAY B)	32	786	25	513	0.95 [0.55, 1.64]
Weakness	Detke 2004 (HMAY A)	2	188	2	86	0.45 [0.06, 3.26]
Weight gain	Detke 2004 (HMAY A); Perahia 2006 (HMAY B)	5	384	1	183	1.71 [0.28, 10.59]
Weight loss	Detke 2004 (HMAY A); Perahia 2006 (HMAY B)	10	384	1	183	2.73 [0.46, 16.26]
Duloxetine versus newer antidepressants						
<i>Duloxetine vs venlafaxine XR</i>						
Anorexia	Perahia 2008 (HMBU)	4	166	10	166	0.39 [0.12, 1.25]
Appetite decreased	Perahia 2008 (HMBU); ID#7999 (HMCQ)	32	325	37	498	1.22 [0.33, 4.47]
Dream activity increased	Perahia 2008 (HMBU)	10	166	6	166	1.71 [0.61, 4.82]
Dyspepsia	ID#7999 (HMCQ)	5	159	14	332	0.74 [0.26, 2.08]
Fatigue	Perahia 2008 (HMBU); ID#7999 (HMCQ)	25	325	29	498	1.34 [0.76, 2.35]
Headache	Perahia 2008 (HMBU); ID#7999 (HMCQ)	65	325	99	498	0.99 [0.69, 1.41]
Palpitations	Perahia 2008 (HMBU)	4	166	10	166	0.39 [0.12, 1.25]
Paraesthesia	Perahia 2008 (HMBU)	9	166	5	166	1.85 [0.61, 5.63]

Adverse event	Study	Duloxetine		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Sexual problems (loss of sexual interest)	ID#7999 (HMCQ)	11	159	18	332	1.30 [0.60, 2.81]
Sweating	Perahia 2008 (HMBU); ID#7999 (HMCQ)	45	325	62	498	1.05 [0.69, 1.59]
Tremor	Perahia 2008 (HMBU); ID#7999 (HMCQ)	21	325	31	498	1.09 [0.61, 1.97]
Upper respiratory tract infection	ID#7999 (HMCQ)	8	159	16	332	1.05 [0.44, 2.50]
Visual problems	ID#7999 (HMCQ)	10	159	20	332	1.05 [0.48, 2.29]