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Escitalopram versus other antidepressive agents for depression

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Abstract

Background—Although pharmacological and psychological interventions are both effective for major depression, antidepressant drugs remain the mainstay of treatment in primary and secondary care settings. During the last 20 years, antidepressant prescribing has risen dramatically in western countries, mainly because of the increasing consumption of selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants, which have progressively become the most commonly prescribed antidepressants. Escitalopram is the pure S-enantiomer of the racemic citalopram.

Objectives—To assess the evidence for the efficacy, acceptability and tolerability of escitalopram in comparison with tricyclics, other SSRIs, heterocyclics and newer agents in the acute-phase treatment of major depression.

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CONTRIBUTIONS OF AUTHORS

AC, CB, TAF, RC and HMG conceived and designed the review. AC, CS, AS and HMG identified and acquired reports of trials, and contacted authors of trials and pharmaceutical industries for additional information. AC, CS and AS extracted data. AC, CS, CB and TAF analysed and interpreted the data. RC, AS, AN and HMG contributed to the interpretation of the data. AC and CS drafted the manuscript. CB, TAF, AS, AN, RC and HMG critically reviewed the manuscript. All authors saw and approved the final version of the manuscript.

DECLARATIONS OF INTEREST

AC, CS, AS, CB, AN, CRC, HMG: none
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Search methods—Electronic databases were searched up to July 2008. Trial databases of drug-approving agencies were hand-searched for published, unpublished and ongoing controlled trials.

Selection criteria—All randomised controlled trials comparing escitalopram against any other antidepressant (including non-conventional agents such as hypericum) for patients with major depressive disorder (regardless of the diagnostic criteria used).

Data collection and analysis—Data were entered by two review authors (double data entry). Responders and remitters to treatment were calculated on an intention-to-treat basis. For dichotomous data, odds ratios (ORs) were calculated with 95% confidence intervals (CI). Continuous data were analysed using standardised mean differences (with 95% CI) using the random effects model.

Main results—Fourteen trials compared escitalopram with another SSRI and eight compared escitalopram with a newer antidepressive agent (venlafaxine, bupropion and duloxetine). Escitalopram was shown to be significantly more effective than citalopram in achieving acute response (OR 0.67, 95% CI 0.50 to 0.87). Escitalopram was also more effective than citalopram in terms of remission (OR 0.53, 95% CI 0.30 to 0.93). Significantly fewer patients allocated to escitalopram withdrew from trials compared with patients allocated to duloxetine, for discontinuation due to any cause (OR 0.62, 95% CI 0.38 to 0.99).

Authors' conclusions—Some statistically significant differences favouring escitalopram over other antidepressive agents for the acute phase treatment of major depression were found, in terms of efficacy (citalopram and fluoxetine) and acceptability (duloxetine). There is insufficient evidence to detect a difference between escitalopram and other antidepressants in early response to treatment (after two weeks of treatment). Cost-effectiveness information is also needed in the field of antidepressant trials. Furthermore, as with most standard systematic reviews, the findings rely on evidence from direct comparisons. The potential for overestimation of treatment effect due to sponsorship bias should also be borne in mind.

Medical Subject Headings (MeSH)

Antidepressive Agents [*therapeutic use]; Citalopram [*therapeutic use]; Depression [*drug therapy]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [*therapeutic use]

MeSH check words

Humans

BACKGROUND

Description of the condition

Major depression is generally diagnosed when a persistent and unreactive 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 (Murray 1997). 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 2007).

Description of the intervention

Although pharmacological and psychological interventions are both effective for major depression, in primary and secondary care settings antidepressant drugs remain the mainstay of treatment (APA 2000; Ellis 2004; NICE 2007) (see below for other references to the relevant evidence). Amongst antidepressants many different agents are available, including tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs, such as venlafaxine, duloxetine and milnacipran), and other newer agents (mirtazapine, reboxetine, bupropion). During the last 20 years, consumption of antidepressant has risen dramatically in western countries, mainly because of the increasing consumption of SSRIs and newer antidepressants, which have progressively become the most commonly prescribed antidepressants (Ciuna 2004; Guaiana 2005). SSRIs are generally better tolerated than TCAs (Barbui 2000), and there is evidence of similar efficacy (Anderson 2000; Geddes 2000; Williams 2000). However, head-to-head comparison have provided contrasting findings. Amitriptyline, for example, may have the edge over SSRIs in terms of efficacy (Guaiana 2003), and individual SSRIs and SNRIs may differ in terms of efficacy and tolerability (Puech 1997; Smith 2002; Hansen 2005; Cipriani 2006).

Escitalopram is the pure S-enantiomer of the racemic citalopram. As for all other antidepressants belonging to the SSRIs class, the mechanism of antidepressant action of escitalopram is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from its inhibition of neuronal re-uptake of serotonin. Escitalopram is at least 100 fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Escitalopram has no or very low affinity for other receptors (alpha- and beta-adrenergic, dopamine (D1-5), histamine (H1-3), muscarinic (M1-5), and benzodiazepine receptors). The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. In vitro studies indicated that CYP3A4 and −2C19 are the primary enzymes involved in the metabolism of escitalopram, however these studies did not reveal an inhibitory effect of escitalopram on CYP2D6.

How the intervention might work

The efficacy of escitalopram as a treatment for major depressive disorder was established in three, 8-week, placebo-controlled studies conducted in outpatients between 18 and 65 years of age who met DSM-IV criteria for major depressive disorder (www.fda.gov). The primary outcome in all three studies was change from baseline to endpoint in the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery 1979). The 10 mg/day and 20 mg/day escitalopram treatment groups showed significantly greater mean improvement compared to placebo on the MADRS. Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics. Among the 715 depressed patients who received escitalopram in placebo-controlled trials, 6% discontinued treatment due to an adverse

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event, compared to 2% of 592 patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day escitalopram was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day escitalopram (4%) and placebo (3%). The most commonly observed adverse events in escitalopram patients (incidence of approximately 5% or greater and approximately twice the incidence as in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, increased sweating, fatigue, and somnolence.

Why it is important to do this review

To shed light on the field of antidepressant trials and treatment of major depressive disorder, a group of researchers agreed to join forces under the rubric of the Meta-Analyses of New Generation Antidepressants Study Group (MANGA Study Group) to systematically review all available evidence for each specific newer antidepressant. As of October 2008, we have completed an individual review for fluoxetine (Cipriani 2005), and published the protocols for venlafaxine (Cipriani 2007a), sertraline (Malvini 2006), fluvoxamine (Omori 2006), citalopram (Imperadore 2007), duloxetine (Nose 2007), milnacipran (Nakagawa 2007), paroxetine (Cipriani 2007b) and mirtazapine (Watanabe 2006). Thus, the aim of the present review is to assess the evidence for the efficacy and tolerability of escitalopram in comparison with TCAs, heterocyclics, other SSRIs and newer antidepressants, including non-conventional agents such as herbal products like hypericum (Linde 2008), in the acute-phase treatment of major depression.

OBJECTIVES

1. To determine the efficacy of escitalopram in comparison with other antidepressive agents for depression in alleviating the acute symptoms of major depressive disorder.
2. To investigate the acceptability of escitalopram in comparison with other antidepressive agents for depression.
3. To investigate the adverse effects of escitalopram in comparison with other antidepressive agents for depression.

METHODS

Criteria for considering studies for this review

Types of studies—Only randomised controlled trials were included. Quasi-randomised trials, such as those allocating by using alternate days of the week, were excluded.

Types of participants—Patients aged 18 or older, of both sexes, with a primary diagnosis of major depression. Studies adopting any standardised criteria to define patients suffering from unipolar major depression were included. Studies from the 1990s onwards were likely to have used DSM-IV (APA 1994) or ICD-10 (WHO 1992) criteria. Earlier studies may had used ICD-9 (WHO 1978), DSM-III (APA 1980) / DSM-III-R (APA 1987) or other diagnostic systems. ICD-9 is not operationalised criteria, because it has only disease names and no diagnostic criteria, so studies using ICD-9 were excluded. However, studies using

Feighner criteria or Research Diagnostic Criteria were included. Studies in which less than 20% of the participants might be suffering from bipolar depression were included, but the validity of this decision was examined in a sensitivity analysis. A concurrent secondary diagnosis of another psychiatric disorder was not considered as an exclusion criterion. A concurrent primary diagnosis of Axis I or II disorders was an exclusion criterion. Antidepressant trials in depressive patients with a serious concomitant medical illness were also excluded.

Types of interventions

Experimental intervention: Escitalopram (as monotherapy). No restrictions on dose, frequency, intensity and duration were applied.

Comparator interventions: All other antidepressive agents in the treatment of acute depression, including:

1. conventional tricyclic ADs (TCAs)
2. heterocyclic antidepressants (e.g. maprotiline)
3. SSRIs (fluoxetine, fluvoxamine, citalopram, paroxetine, sertraline)
4. newer antidepressants (SNRIs such as venlafaxine, duloxetine, milnacipran; MAOIs or newer agents such as mirtazapine, bupropion, reboxetine; and non-conventional ADs, such as herbal products - e.g. hypericum).

No restrictions on dose, frequency, intensity and duration were applied.

Other types of psychopharmacological agent such as anxiolytics, anticonvulsants, antipsychotics or mood-stabilizers were excluded. Trials in which escitalopram was used as an augmentation strategy were also excluded

Types of outcome measures

Primary outcomes: Number of patients who responded to treatment, showing a reduction of at least 50% on the Hamilton Depression Scale (HAM-D) (Hamilton 1960) or MADRS (Montgomery 1979), or any other depression scale, or “much or very much improved” (score 1 or 2) on CGI-Improvement (Guy 1970). All response rates were calculated out of the total number of randomised patients. Where more than one criterion was provided, we preferred the HAM-D for judging response. We used the HAM-D whenever possible, even when we needed to impute SDs or response rates according to the procedures described in the Methods section below.

When studies reported response rates at various time points of the trial, we decided a priori to subdivide the treatment indices as follows:

1. Early response: between 1 and 4 weeks, the time point closest to 2 weeks was given preference.
2. Acute phase treatment response: between 6 and 12 weeks, the time point given in the original study as the study endpoint was given preference.

3. Follow-up response: between 4 and 6 months, the time point closest to 24 weeks was given preference.

The acute phase treatment response, i.e. between 6 and 12 weeks, was our primary outcome of interest.

Secondary outcomes

1. Number of patients who achieved remission. The cut-off point for remission was set a priori (i) at 7 or less on the 17-item HAM-D and at 8 or less for all the other longer versions of HAM-D, or (ii) at 12 or less on the MADRS (Zimmerman 2004), or (iii) "not ill or borderline mentally ill" (score 1 or 2) on CGI-Severity (Guy 1970). All remission rates was calculated out of the total number of randomised patients. Where two or more were provided, we preferred the HAM-D for judging remission.
2. Change scores from baseline to the time point in question (early response, acute phase response, or follow-up response as defined above) on HAM-D, or MADRS, or any other depression scale. We applied a looser form of ITT analysis, whereby all the patients with at least one post-baseline measurement were represented by their last observations carried forward.
3. Social adjustment, social functioning, including the Global Assessment of Function (Luborsky 1962) scores
4. Health-related quality of life: we limited ourselves to SF-12/SF-36 (Ware 1993), HoNOS (Wing 1994) and WHOQOL (WHOQOL Group 1998).
5. Costs to health care services
6. Acceptability

   Acceptability was evaluated using the following outcome measures:

   a. Number of patients who dropped out during the trial as a proportion of the total number of randomised patients - Total drop out rate
   b. Number of patients who dropped out due to inefficacy during the trial as a proportion of the total number of randomised patients
      - Drop out rates due to inefficacy
   c. Number of patients who dropped out due to side effects during the trial as a proportion of the total number of randomised patients
      - Drop out rates due to side effects.
7. Tolerability

Tolerability was evaluated using the following outcome measures:

1. Total number of patients experiencing at least some side effects.
2. Total number of patients experiencing the following specific side effects were sought for:

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a. Agitation/anxiety
b. Constipation
c. Diarrhoea
d. Dry mouth
e. Hypotension
f. Insomnia
g. Nausea
h. Sleepiness/drowsiness
i. Urination problems
j. Vomiting
k. Deaths, suicide and suicidality

In order not to miss any relatively rare or unexpected yet important side effects, in the data extraction phase, we collected all side effects data reported in the literature and discussed ways to summarise them post hoc.

Search methods for identification of studies

Electronic searches—See: Cochrane Collaboration Depression, Anxiety and Neurosis Group (CCDAN) methods used in reviews.

Electronic Databases—CCDANCTR-Studies were searched using the following search strategy:

Diagnosis = Depress* or Dysthymi* or “Adjustment Disorder*” or “Mood Disorder*” or “Affective Disorder” or “Affective Symptoms” and Intervention = Escitalopram

CCDANCTR-References were searched using the following search strategy:

Keyword = Depress* or Dysthymi* or “Adjustment Disorder*” or “Mood Disorder*” or “Affective Disorder” or “Affective Symptoms” and Free-Text = Escitalopram

An additional Medline search was carried out (update: July 2008). 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 (EMEA) in the EU, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Therapeutic Goods Administration (TGA) in Australia) and ongoing trial registers (clinicaltrials.gov in the USA, ISRCTN and National Research Register in the UK, Nederlands Trial Register in the Netherlands, EUDRACT in the EU, UMIN-CTR in Japan and the Australian Clinical Trials Registry in Australia) were searched for published, unpublished and ongoing controlled trials (update: July 2008).

Searching other resources

1) Handsearches: Appropriate journals and conference proceedings relating to escitalopram treatment for depression were 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 which 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. The references of all included studies were checked via Science Citation Index for articles which had cited the included study.

Data collection and analysis

Selection of studies—Studies relating to escitalopram generated by the electronic search of CCDANCTR-Studies were scanned by one review author (HMG). Those studies that met the following criteria constituted the preliminary list and their full texts were retrieved:.

The rough inclusion criteria were:

1. Randomised trial
2. Comparing escitalopram against any other antidepressant
3. Patients with major depression, regardless of the diagnostic criteria used.

Studies relating to escitalopram generated by the search strategies of CCDANCTR-References and the other complementary searches were checked independently by the CCDAN Trials Search Coordinator (HMG), who is an author of this review, and another review author (AC, AS or CS) to see if they met the rough inclusion criteria, firstly based on the title and abstracts. All the studies rated as possible candidates by either of the two reviewers were added to the preliminary list and the full texts were retrieved. All the full text articles in this preliminary list was then assessed by two review authors (AC, AS or CS) independently to see if they met the strict inclusion criteria. If the raters disagreed, the final rating were made by consensus with the involvement (if necessary) of another member of the review group. Non-congruence in selection of trials was reported as percentage disagreement. Considerable care was taken to exclude duplicate publications.

Data extraction and management—One review author (CS) first extracted data concerning participant characteristics (age, sex, depression diagnosis, comorbidity, depression severity, antidepressant treatment history for the index episode, study setting), intervention details (intended dosage range, mean daily dosage actually prescribed, co-intervention if any, escitalopram as investigational drug or as comparator drug, sponsorship) and 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 there were any discrepancies, a second review author (AC) intervened and the agreed-upon results were used in the review as well as fed back to the authors of the completed reviews.

Assessment of risk of bias in included studies—We used the Cochrane risk-of-bias tool as recommended in RevMan 5.0.0. This instrument consists of six items. Two of the items assess the strength of the randomisation process in preventing selection bias in the assignment of participants to interventions: adequacy of sequence generation and allocation concealment. The third item (blinding) assesses the influence of performance bias on the study results. The fourth item assesses the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes. It requires a comparison of published data with trial protocols, when such are available. The final item refers to other sources of bias that are relevant in certain circumstances, for example, in relation to trial design (methodologic issues such as those related to crossover designs and early trial termination) or setting.

Two review authors (AC, CB) assessed risk of bias in each trial independently, in accordance with the Cochrane Handbook (Higgins 2008). Where inadequate details of allocation concealment and other characteristics of trials were provided, the trial authors were contacted in order to obtain further information. If the raters disagreed the final rating was made by consensus with the involvement (if necessary) of another member of the review group. The ratings were also compared with those in the completed reviews of individual antidepressants in the Cochrane Library. If here were any discrepancies, they were fed back to the authors of the completed reviews.

Measures of treatment effect—Data were checked and entered into Review Manager 5 software by two review authors (AC, CS) (double data entry). For dichotomous, or event-like data, odds ratios (OR) were calculated with 95% confidence intervals. Continuous data were analysed using weighted mean differences (with 95% confidence intervals) or standardised mean differences (where different measurement scales are used) using the random effects model.

Unit of analysis issues—For trials which had a crossover design only results from the first randomisation period were considered. If the trial was a three (or more)-armed trial involving a placebo arm, the data were extracted from the placebo arm as well.

Dealing with missing data—Responders and remitters to treatment were calculated on the intention-to-treat (ITT) basis: drop-outs were always included in this analysis. Where participants had withdraw from the trial before the endpoint, it was assumed they would have experienced the negative outcome by the end of the trial (e.g. failure to respond to treatment). When there were missing data and the method of “last observation carried forward” (LOCF) had been used to do an ITT analysis, then the LOCF data were used, with due consideration of the potential bias and uncertainty introduced. When dichotomous or continuous outcomes were not reported, trial authors were asked to supply the data.

When only the SE or t-statistics or p values were reported, SDs were calculated according to Altman (Altman 1996). In the absence of supplemental data from the authors, the SDs of the HAM-D (or any other depression scale) and response/remission rates were calculated

according to validated imputation methods (Furukawa 2005; Furukawa 2006). We examined the validity of these imputations in sensitivity analyses.

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-squared statistic (Higgins 2003) (I-squared equal to or more than 50% was considered indicative of heterogeneity) and by visual inspection of forest plots.

Assessment of reporting biases—Funnel plot analysis was performed to check for existence of small study effects, including publication bias.

Data synthesis—The primary analysis used a random effects model OR, which had the highest generalisability in our 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 ratio (RR). Material differences between the models were reported. Fixed effect analyses were done 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.

Subgroup analysis and investigation of heterogeneity—Subgroup analyses were performed and interpreted with caution because multiple analyses can lead to false positive conclusions (Oxman 1992). However, we performed the following subgroup analyses, where possible, for the following a priori reasons:

1. Escitalopram dosing (fixed low dosage, fixed standard dosage, fixed high dosage; flexible low dosage, flexible standard dosage, flexible high dosage), because there was evidence to suspect that low dosage antidepressant might be associated with better outcomes both in terms of effectiveness and side effects than standard or high dosage antidepressants (Bollini 1999; Furukawa 2002b) and also because fixed versus flexible dosing schedule might affect estimates of treatment effectiveness (Khan 2003). In the case of escitalopram, based on the Defined Daily Dosage by World Health Organisation (WHO), low dosage referred to <10, standard dosage to >10 but <20, and high dosage to >20 mg/day.
2. Comparator dosing (low effective range, medium to high effective range), as it was easy to imagine that there were greater chances of completing the study on the experimental drug than on the comparator drug that was increased to the maximum dosage.
3. Depression severity (severe major depression, moderate/mild major depression).
4. Treatment settings (psychiatric inpatients, psychiatric outpatients, primary care).
5. Elderly patients (>65 years of age), separately from other adult patients.

Sensitivity analysis—The following sensitivity analyses were planned a priori. By limiting included studies to those with higher quality, we examined if the results changed, and checked for the robustness of the observed findings.

1. Excluding trials with unclear concealment of random allocation and/or unclear double blinding.
2. Excluding trials whose drop out rate was greater than 20%.
3. Performing the worst case scenario ITT (all the patients in the experimental group experience the negative outcome and all those allocated to the comparison group experience the positive outcome) and the best case scenario ITT (all the patients in the experimental group experience the positive outcome and all those allocated to the comparison group experience the negative outcome).
4. Excluding trials for which the response rates had to be calculated based on the imputation method (Furukawa 2005) and those for which the SD had to be borrowed from other trials (Furukawa 2006).
5. Examination of “wish bias” (also called “optimism bias”) by comparing escitalopram as investigational drug vs escitalopram as comparator, as there was evidence to suspect that a new antidepressant might perform worse when used as a comparator than when used as an experimental agent (Barbui 2004).
6. Excluding studies funded by the pharmaceutical company marketing escitalopram. This sensitivity analysis was particularly important in view of the recent repeated findings that funding strongly affects outcomes of research studies (Als-Nielsen 2003; Bhandari 2004; Lexchin 2003; Montgomery 2004; Perlis 2005; Procyshyn 2004) and because industry sponsorship and authorship of clinical trials were increasing over 20 years (Buchkowsky 2004).

If subgroups within any of the subgroup or sensitivity analyses turned out to be significantly different from one another, we ran meta-regression for exploratory analyses of additive or multiplicative influences of the variables in question. 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.

Results of the search—The search yielded 52 references of potentially eligible studies. After exclusion of papers that were not relevant (because they mainly were non-randomised studies or reviews), 19 randomised controlled trials were included in the present review. Three further randomised controlled trials were found in the web-based clinical trial register of the pharmaceutical industry manufacturing escitalopram and were included in the pool of included studies. Therefore, a total of 22 trials were included in the review.

In the presentation of the following analyses, a post-hoc decision was made to present all SSRIs (with sub-totals) together in one group, and SNRIs and newer antidepressant agents (without subtotals) together in a second group (see graphs). Fourteen trials (64%) compared escitalopram with another SSRI and eight (36%) compared escitalopram with a newer antidepressant (venlafaxine, bupropion and duloxetine). Neither trials comparing escitalopram with TCAs or MAOIs nor cross-over design studies were retrieved by the comprehensive search. In this review all studies were multicentre, randomised, double-blind trials (nine were three-arm, placebo-controlled trials).

Included studies

Design

Length of the studies

Escitalopram versus other SSRIs: In 11 studies the follow-up was 8 weeks (Alexopoulos 2004; Baldwin 2006; Burke 2002; Kasper 2005; Kennedy 2005; Lepola 2003; Mao 2008; Moore 2005; SCT-MD-02; SCT-MD-09; Ventura 2007). One study was a 6-week trial (Yevtushenko 2007) and in two studies the follow-up lasted up to 24 weeks (Boulenger 2006; Colonna 2005).

Escitalopram versus newer antidepressants: Seven studies were 8-week trials (Bielski 2004; Clayton (AK130926); Clayton (AK130927); Khan 2007; Montgomery 2004; Nierenberg 2007; SCT-MD-35) and one study was a 24-week trial (Wade 2007).

Sample size

Escitalopram versus other SSRIs: The mean of participants per study was 280.8 (SD 103.9), with a minimum sample size of 30 (SCT-MD-09) and a maximum of 459 (Boulenger 2006).

Escitalopram versus newer antidepressants: The mean of participants was 307.1 (SD 101.3), ranging between 202 (Bielski 2004) and 547 (Nierenberg 2007).

Setting

Escitalopram versus other SSRIs: In 11 studies the participants were outpatients (Alexopoulos 2004; Baldwin 2006; Boulenger 2006; Burke 2002; Colonna 2005; Kennedy 2005; Moore 2005; SCT-MD-02; SCT-MD-09; Ventura 2007; Yevtushenko 2007). In one study (Lepola 2003) participants were recruited in primary care. In two studies (Kasper 2005; Mao 2008) both outpatients and inpatients were eligible. In Kasper 2005, patients were recruited both in general practice and specialist settings.

Escitalopram versus other antidepressants: In 7 studies the participants were outpatients (Bielski 2004; Clayton (AK130926); Clayton (AK130927); Khan 2007; Nierenberg 2007; SCT-MD-35; Wade 2007). In Montgomery 2004 patients were recruited in primary care.

Participants

Age

Escitalopram versus other SSRIs: In eight studies patients over 65 years were excluded (Alexopoulos 2004; Baldwin 2006; Burke 2002; Colonna 2005; Lepola 2003; Mao 2008; SCT-MD-09; Yevtushenko 2007). Five studies included patients over 65 years (Boulenger 2006; Kennedy 2005; Moore 2005; SCT-MD-02; Ventura 2007). One study (Kasper 2005) included only elderly patients (over 65 years).

Escitalopram versus newer antidepressants: In two studies patients over 65 years were excluded (Bielski 2004; Wade 2007). Four studies included patients over 65 years (Khan 2007; Montgomery 2004; Nierenberg 2007; SCT-MD-35). In two studies age range was not specified (Clayton (AK130926); Clayton (AK130927)).

Diagnosis: All the studies enrolled patients suffering from DSM-IV criteria for major depressive disorder.

Interventions

Escitalopram versus other SSRIs: In six studies escitalopram was compared with citalopram (Burke 2002; Colonna 2005; Lepola 2003; Moore 2005; SCT-MD-02; Yevtushenko 2007), in four with fluoxetine (Kasper 2005; Kennedy 2005; Mao 2008; SCT-MD-09), in two with paroxetine (Baldwin 2006; Boulenger 2006) and in the remaining two with sertraline (Alexopoulos 2004; Ventura 2007). Five studies included a placebo arm (Alexopoulos 2004; Burke 2002; Kasper 2005; Lepola 2003; SCT-MD-02). One study (Burke 2002) presented a comparison between four arms: escitalopram 10mg/day, escitalopram 20mg/day, citalopram and placebo.

Escitalopram versus newer antidepressants: Three studies compared escitalopram with bupropion XR (Clayton (AK130926); Clayton (AK130927); SCT-MD-35), three with duloxetine (Khan 2007; Nierenberg 2007; Wade 2007) and two with venlafaxine XR (Bielski 2004; Montgomery 2004). Four studies included a placebo arm (Clayton (AK130926); Clayton (AK130927); Nierenberg 2007; SCT-MD-35). One study (SCT-MD-35) presented a comparison between four arms: escitalopram 4mg/day, bupropion XR 150mg/day, placebo and a combination of escitalopram 4mg/day and bupropion XR 150mg/day.

Dosage of study drugs: In 21 out of 22 studies the dosage of escitalopram was within the therapeutic dosage (10 to 20 mg/day). In one study (SCT-MD-35) the escitalopram dosage was set at 4 mg/day (fixed dose). Eleven trials used a fixed- and the remaining eleven a flexible-dosage regimen. The use of a fixed- or a flexible-dose regimen was consistent among comparisons within the same study in the great majority of included trials. However, in three out of 22 studies one of the two compounds used a fixed-dose while the other used a flexible-dose design (Burke 2002; Khan 2007; Ventura 2007).

Primary Outcomes

Escitalopram versus other SSRIs: The primary outcome used in the great majority of studies was change from baseline on MADRS. One study (Mao 2008) used the change on the HAM-D-17 total score and another trial (SCT-MD-09) evaluated the effects of escitalopram and fluoxetine on sleep in depressed patients using the number of awakenings (polysomnogram) as the primary outcome. The latter study lasted only five weeks, did not evaluate efficacy and has been included in the present review only for early discontinuation and tolerability outcomes (side-effect profile).

Escitalopram versus other antidepressants: Five studies used the change from baseline on MADRS (Bielski 2004; Khan 2007; Montgomery 2004; SCT-MD-35; Wade 2007) as the primary outcome and one used change on HAMD-17 (Nierenberg 2007). In studies by Clayton (Clayton (AK130926); Clayton (AK130927)) sexual functioning was considered the primary outcome and depression was rated as mean change on HAMD-17.

Response Rate

Escitalopram versus other SSRIs: In nine studies a decrease from baseline to endpoint of at least 50% in rating scale total score (either on MADRS or on HAM-D) was used to define “response” (Baldwin 2006; Boulenger 2006; Burke 2002; Colonna 2005; Kasper 2005; Lepola 2003; Mao 2008; Moore 2005; Ventura 2007). The four remaining studies (Alexopoulos 2004; Kennedy 2005; SCT-MD-02; SCT-MD-09) provided only continuous data and therefore response rates were imputed (see Methods).

Escitalopram versus newer antidepressants: In four studies, a decrease from baseline to endpoint of at least 50% in MADRS total score was used to define “response” (Bielski 2004; Khan 2007; Montgomery 2004; Wade 2007). In three studies a decrease from baseline to endpoint of at least 50% in HAMD-17 total score was used for defining “response” (Clayton (AK130926); Clayton (AK130927); Nierenberg 2007). In one study (SCT-MD-35) only continuous data were available and therefore response rate was imputed (see Methods).

Remission Rate

Escitalopram versus other SSRIs: Six studies used MADRS to assess remission rate (Baldwin 2006; Boulenger 2006; Colonna 2005; Kasper 2005; Lepola 2003; Moore 2005). One study used HAMD-17 (Ventura 2007). Five studies did not report remission rate (Alexopoulos 2004; Burke 2002; Kennedy 2005; SCT-MD-02; SCT-MD-09). However, considering that continuous outcomes were available, remission rates were imputed (see Methods)

Escitalopram versus newer antidepressants: Six studies used HAMD-17 (Bielski 2004; Clayton (AK130926); Clayton (AK130927); Khan 2007; Nierenberg 2007; Wade 2007) and one used MADRS (Montgomery 2004) to assess remission rate. One study (SCT-MD-35) did not report dichotomous data remission rate, so remission rate was imputed using continuous outcomes (see Methods)

Sponsorship

Escitalopram versus other SSRIs: All the studies were sponsored by the drug company marketing escitalopram.

Escitalopram versus newer antidepressants: Five studies were sponsored by the drug company marketing escitalopram (Bielski 2004; Khan 2007; Montgomery 2004; SCT-MD-35; Wade 2007). Two studies were sponsored by the drug company marketing bupropion XR (Clayton (AK130926); Clayton (AK130927)). One study was sponsored by the drug company marketing duloxetine (Nierenberg 2007).

Excluded studies—Thirty-three references of potentially eligible studies were excluded after checking titles and abstracts. Of those, 21 were reviews, nine were non-randomised studies and three were duplicates.

Risk of bias in included studies

See Figure 1 and Figure 2 for a graphical summary of methodological quality for the 22 included studies, based on the six risk of bias domains.

Allocation—Only four studies reported sufficient details on allocation concealment (Baldwin 2006; Boulenger 2006; Colonna 2005; Wade 2007).

Blinding—All studies were reported to be double-blind trials, however only five studies reported sufficient details on blinding (Baldwin 2006; Boulenger 2006; Colonna 2005; Wade 2007; Yevtushenko 2007)

Incomplete outcome data—Only three studies reported incomplete outcome data (Clayton (AK130926); Clayton (AK130927); SCT-MD-09).

Selective reporting—Only eight studies were indicated to be free from selective reporting (Alexopoulos 2004; Bielski 2004; Boulenger 2006; Clayton (AK130926); Clayton (AK130927); Khan 2007; Ventura 2007; Yevtushenko 2007).

Other potential sources of bias—The large majority of included studies were sponsored by the manufacturer of escitalopram.

Effects of interventions

Some statistically significant differences in efficacy, acceptability and tolerability were found and details are listed below. The results are reported comparison by comparison (dividing SSRIs from newer antidepressants) and the forest plots are organised according to the relevance of outcomes, as reported in the review protocol. For adverse events, all the information about adverse events specified in the review protocol are reported (either statistically or non-statistically significant). However, remaining adverse events are only reported when statistically significant (non-statistically significant results about adverse events are presented in Table 1).

1. ESCITALOPRAM versus OTHER SSRIs

A. ESCITALOPRAM versus CITALOPRAM

PRIMARY OUTCOME

a) Acute phase treatment (6 to 12 weeks): There was a statistically significant difference with escitalopram being more effective than citalopram (OR 0.67, 95% CI 0.50 to 0.89, p = 0.006; 6 studies, 1823 participants) (see Figure 3).

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

c) Follow-up response (16 to 24 weeks): There was no statistically significant difference between escitalopram and citalopram (OR 0.96, 95% CI 0.60 to 1.56, p = 0.88; 1 study, 357 participants) (Analysis 3.1).

SECONDARY OUTCOMES

a) Acute phase treatment (6 to 12 weeks): There was a statistically significant difference with escitalopram being more effective than citalopram (OR 0.57, 95% CI 0.36 to 0.90, p = 0.02; 6 studies, 1823 participants) (see Figure 4). Test for heterogeneity was statistically significant: $Tau^2 = 0.25$; $Chi^2 = 25.12$, df = 5 (P<0.00001); I^2=80%. The heterogeneity arose because of the extreme result in the Yevtushenko 2007 trial.

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

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

a) Acute phase treatment: between 6 and 12 weeks: Escitalopram was found to be more efficacious than citalopram in reduction of depressive symptoms (SMD −0.17, 95% CI −0.30 to −0.04, p = 0.009; 5 studies, 1392 participants) (see Figure 5).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: No data available.

- **a.** No statistically significant difference was found in terms of discontinuation due to any cause (OR 0.78, 95% CI 0.56 to 1.10, p = 0.16; 6 studies, 1823 participants) (see Figure 6).
- **b.** No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 0.74, 95% CI 0.27 to 2.03, p = 0.56; 5 studies, 1604 participants) (see Figure 7).
- **c.** No statistically significant difference was found in terms of discontinuation due to side effects (OR 0.79, 95% CI 0.47 to 1.31, p = 0.36; 5 studies, 1604 participants) (see Figure 8).

7) TOLERABILITY: Total number of patients experiencing at least one side effect

There was no evidence that escitalopram was associated with a smaller or higher rate of adverse events than citalopram (OR 0.79, 95% CI 0.58 to 1.07, p = 0.12; 6 studies, 1802 participants) (Analysis 10.1).

Total number of patients experiencing a specific side effect (only figures for statistically significant differences were reported in the text)

a) Agitation/Anxiety: There was no evidence that escitalopram was associated with a higher or less rate of participants experiencing agitation/anxiety than citalopram (Analysis 11.1).

b) Constipation: No difference was found between escitalopram and citalopram in terms of number of participants experiencing constipation (Analysis 12.1)

c) Diarrhoea: No difference was found between escitalopram and citalopram in terms of number of participants experiencing diarrhoea (Analysis 13.1).

d) Dry mouth: No difference was found between escitalopram and citalopram in terms of number of participants experiencing dry mouth (Analysis 14.1).

e) Hypotension: A single case of hypotension was reported in one study (Moore 2005) and so there was no statistically significant difference between escitalopram and citalopram (Analysis 15.1).

f) Insomnia: There was no evidence that escitalopram was associated with a higher or less rate of participants experiencing insomnia than citalopram (Analysis 16.1).

g) Nausea: There was no evidence that escitalopram was associated with a higher or less rate of participants experiencing nausea than citalopram (Analysis 17.1).

h) Urination problems: No data reported.

i) Sleepiness/drowsiness: There was no evidence that escitalopram was associated with a higher or less rate of participants experiencing sleepiness than citalopram (Analysis 18.1).

j) Vomiting: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing vomiting than citalopram (Analysis 19.1).

k) Deaths, suicide and suicidality: One patient developed suicidal ideation/tendency (in the escitalopram group) (Analysis 31.1), a total of nine patients attempted suicide (six with escitalopram and three with citalopram) (Analysis 31.2) and one patient died (in the citalopram group) (Analysis 31.4), which was by suicide (Analysis 31.3). However, none of these differences were statistically significant.

l) Other adverse events: Escitalopram was associated with a lower rate of participants experiencing jitteriness than citalopram (OR 0.16, 95% CI 0.03 to 0.82, p = 0.03; 1 trial, 369 participants (Analysis 25.1). No statistically significant differences were found for dizziness (Analysis 20.1), fatigue (Analysis 21.1), flu syndrome (Analysis 22.1), headache (Analysis 23.1), impotence (Analysis 24.1), lethargy/sedation (Analysis 26.1), decreased libido (Analysis 27.1), pain (Analysis 28.1, Analysis 28.2, Analysis 28.3), increased sweating (Analysis 29.1) or yawning (Analysis 30.1).

B. ESCITALOPRAM versus FLUOXETINE

PRIMARY OUTCOME

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than fluoxetine in the acute phase of treatment (OR 0.81, 95% CI 0.60 to 1.10, p = 0.17; 3 studies, 783 participants) (see Figure 3).

b) Early response (1 to 4 weeks): Only one trial reported data on the early phase of treatment and the difference was not statistically significant (OR 1.15, 95% CI 0.52 to 2.56, p = 0.73; 1 study, 240 participants) (Analysis 2.1).

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

SECONDARY OUTCOMES

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than fluoxetine in terms of remission of symptoms (OR 0.86, 95% CI 0.65 to 1.15, p = 0.32; 3 studies, 783 participants) (see Figure 4).

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

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

a) Acute phase treatment: between 6 and 12 weeks: Escitalopram was found to be more efficacious than fluoxetine in reduction of depressive symptoms (SMD −0.17, 95% CI −0.32 to −0.03, p = 0.02; 3 studies, 759 participants) (see Figure 5).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: No data available.

- **a.** No statistically significant difference was found in terms of discontinuation due to any cause (OR 0.89, 95% CI 0.51 to 1.55, p = 0.68; 4 studies, 813 participants) (see Figure 6).
- **b.** No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 0.57, 95% CI 0.15 to 2.15, p = 0.41; 4 studies, 813 participants) (see Figure 7).
- **c.** No statistically significant difference was found in terms of discontinuation due to side effects (OR 0.75, 95% CI 0.44 to 1.28, p = 0.29; 4 studies, 813 participants) (see Figure 8).

7) TOLERABILITY: Total number of patients experiencing at least one side effect

There was no evidence that escitalopram was associated with a less or higher rate of adverse events than fluoxetine (OR 0.80, 95% CI 0.59 to 1.07, p = 0.13; 4 studies, 804 participants) (Analysis 10.1).

Total number of patients experiencing specific side effects (only figures for statistically significant differences are reported in the text - for full details see graphs)

a) Agitation/Anxiety: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing agitation/anxiety than fluoxetine (Analysis 11.1).

b) Constipation: No difference was found between escitalopram and fluoxetine in terms of number of participants experiencing constipation (Analysis 12.1).

c) Diarrhoea: No difference was found between escitalopram and fluoxetine in terms of number of participants experiencing diarrhoea (Analysis 13.1).

d) Dry mouth: No difference was found between escitalopram and fluoxetine in terms of number of participants experiencing dry mouth (Analysis 14.1).

e) Hypotension: No data available

f) Insomnia: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing insomnia than fluoxetine (Analysis 16.1).

g) Nausea: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing nausea than fluoxetine (Analysis 17.1).

h) Urination problems: No data reported.

i) Sleepiness/drowsiness: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing sleepiness than fluoxetine (Analysis 18.1).

j) Vomiting: No data reported.

k) Deaths, suicide and suicidality: Two patients attempted suicide (one with escitalopram and one with fluoxetine) (Analysis 31.2). Neither of these differences were statistically significant. Overall three patients died, two in the fluoxetine group and one in the escitalopram group (Analysis 31.4) (this patient committed suicide) (Analysis 31.3). No data about suicidal tendency/ideation were reported.

l) Other adverse events: No statistically significant differences were found for dizziness (Analysis 20.1), fatigue (Analysis 21.1), headache (Analysis 23.1), impotence (Analysis 24.1), libido decreased (Analysis 27.1) or pain (Analysis 28.1, Analysis 28.2).

C. ESCITALOPRAM versus PAROXETINE

PRIMARY OUTCOME

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than paroxetine in terms of response to treatment (OR 0.89, 95% CI 0.61 to 1.32, p = 0.57; 2 studies, 784 participants) (see Figure 3).

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

c) Follow-up response (16 to 24 weeks): There was no statistically significant difference between escitalopram and paroxetine (OR 0.73, 95% CI 0.47 to 1.15, p = 0.17; 1 study, 459 participants) (Analysis 3.1).

SECONDARY OUTCOMES

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than paroxetine in terms of remission of symptoms (OR 0.87, 95% CI 0.45 to 1.68, p = 0.67; 2 studies, 784 participants) (see Figure 4).

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

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

(a) Acute phase treatment: between 6 and 12 weeks: There was no evidence that escitalopram was more or less efficacious than paroxetine in reduction of depressive symptoms (SMD −0.05, 95% CI −0.36 to 0.26, p = 0.76; 2 studies, 776 participants) (see Figure 5).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: No data available.

- **a.** No statistically significant difference was found in terms of discontinuation due to any cause (OR 0.68, 95% CI 0.36 to 1.29, p = 0.24; 2 studies, 784 participants) (see Figure 6).
- **b.** No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 1.39, 95% CI 0.17 to 11.44, p = 0.76; 2 studies, 784 participants) (see Figure 7).
- **c.** No statistically significant difference was found in terms of discontinuation due to side effects (OR 0.70, 95% CI 0.25 to 1.96, p = 0.50; 2 studies, 784 participants) (see Figure 8).

7) TOLERABILITY: Total number of patients experiencing at least one side effect

There was no evidence that escitalopram was associated with a smaller or larger rate of adverse events than paroxetine (OR 0.78, 95% CI 0.52 to 1.17, p = 0.23; 1 study, 454 participants) (Analysis 10.1).

Total number of patients experiencing a specific side effect (only figures for statistically significant differences were reported in the text)

a) Agitation/Anxiety: No data reported.

b) Constipation: No difference was found between escitalopram and paroxetine in terms of number of participants experiencing constipation (Analysis 12.1).

c) Diarrhoea: No difference was found between escitalopram and paroxetine in terms of number of participants experiencing diarrhoea (Analysis 13.1).

d) Dry mouth: No difference was found between escitalopram and paroxetine in terms of number of participants experiencing dry mouth (Analysis 14.1).

e) Hypotension: No data reported.

f) Insomnia: No difference was found between escitalopram and paroxetine in terms of number of participants experiencing insomnia (Analysis 16.1).

g) Nausea: There was no evidence that paroxetine was associated with a higher or lower rate of participants experiencing nausea than escitalopram (Analysis 17.1).

h) Urination problems: No data reported.

i) Sleepiness/drowsiness: No data reported.

j) Vomiting: No data reported.

k) Deaths, suicide and suicidality: Neither deaths, nor completed or attempted suicides were reported.

l) Other adverse events: No statistically significant differences were found for dizziness (Analysis 20.1), headache (Analysis 23.1) or increased sweating (Analysis 24.1).

D. ESCITALOPRAM versus SERTRALINE

PRIMARY OUTCOME

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was less or more efficacious than sertraline in terms of response to treatment in the acute phase (OR 1.06, 95% CI 0.73 to 1.53, p = 0.76; 2 studies, 489 participants) (see Figure 3).

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

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

SECONDARY OUTCOMES

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was less or more efficacious than sertraline in terms of remission of symptoms (OR 1.16, 95% CI 0.81 to 1.67, p = 0.42; 2 studies, 489 participants (see Figure 4).

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

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

a) Acute phase treatment: between 6 and 12 weeks: There was no evidence that escitalopram was less or more efficacious than sertraline in reduction of depressive symptoms (SMD 0.02, 95% CI −0.16 to 0.20, p = 0.85; 2 studies, 477 participants) (see Figure 5).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: No data available.

a. No statistically significant difference was found in terms of discontinuation due to any cause (OR 1.24, 95% CI 0.78 to 1.97, p = 0.37; 2 studies, 489 participants) (see Figure 6).

b. No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 3.09, 95% CI 0.32 to 30.08, p = 0.33; 1 study, 274 participants) (see Figure 7).

c. No statistically significant difference was found in terms of discontinuation due to side effects (OR 1.08, 95% CI 0.35 to 3.37, p = 0.89; 2 studies, 489 participants) (see Figure 8).

6) TOLERABILITY: Total number of patients experiencing at least one side effects

There was no evidence that escitalopram was associated with a smaller or larger rate of adverse events than sertraline (OR 0.62, 95% CI 0.33 to 1.19, p = 0.15; 2 studies, 483 participants) (Analysis 10.1).

Total number of patients experiencing a specific side effect (only figures for statistically significant differences were reported in the text)

a) Agitation/Anxiety: No data reported.

b) Constipation: No data reported.

c) Diarrhoea: There was evidence that escitalopram was associated with a lower rate of participants experiencing diarrhoea than sertraline (OR 0.49, 95% CI 0.28 to 0.84, p = 0.009; 2 trials, 483 participants) (Analysis 13.1).

d) Dry mouth: No difference was found between escitalopram and sertraline in terms of number of participants experiencing dry mouth (Analysis 14.1).

e) Hypotension: No data reported.

f) Insomnia: No difference was found between escitalopram and sertraline in terms of number of participants experiencing insomnia (Analysis 16.1).

g) Nausea: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing nausea than sertraline (Analysis 17.1).

h) Urination problem: No data reported.

i) Sleepiness/drowsiness: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing sleepiness/drowsiness than sertraline (Analysis 18.1).

j) Vomiting: No data reported.

k) Deaths, suicide and suicidality: Neither deaths, nor completed or attempted suicides were reported.

l) Other adverse events: Although not statistically significant, there was some evidence in one study (Ventura 2007) that escitalopram was associated with a higher rate of participants experiencing lethargy/sedation than sertraline (OR 3,72, 95% CI 0.99 to 13.94, p = 0.05; 1

trial, 212 participants). No statistically significant differences were found for fatigue (Analysis 21.1), headache (Analysis 22.1), impotence (Analysis 23.1), lethargy/sedation (Analysis 26.1), decreased libido (Analysis 27.1) or increased sweating (Analysis 29.1).

2) ESCITALOPRAM versus NEWER ANTIDEPRESSANTS

A. ESCITALOPRAM versus BUPROPION

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more efficacious than bupropion in terms of response to treatment in the acute phase (OR 0.91, 95% CI 0.69 to 1.20, p = 0.50; 3 studies, 842 participants) (see Figure 9).

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

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

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more efficacious than bupropion in terms of remission of depressive symptoms (OR 0.94, 95% CI 0.67 to 1.32, p = 0.72; 3 studies, 842 participants) (see Figure 10).

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

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

a) Acute phase treatment: between 6 and 12 weeks: There was no evidence that escitalopram was more efficacious than bupropion in reduction of depressive symptoms (SMD −0.08, 95% CI −0.22 to 0.05, p = 0.23; 3 studies, 793 participants) (see Figure 11).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: No data available.

- **a.** No statistically significant difference was found in terms of discontinuation due to any cause (OR 1.02, 95% CI 0.75 to 1.39, p = 0.90; 3 studies, 842 participants) (see Figure 12)
- **b.** No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 0.11, 95% CI 0.01 to 2.02, p = 0.14; 1 study, 276 participants) (see Figure 13)
- **c.** No statistically significant difference was found in terms of discontinuation due to side effects (OR 0.65, 95% CI 0.25 to 1.65, p = 0.36; 3 studies, 842 participants) (see Figure 14)

7) TOLERABILITY: Total number of patients experiencing at least one side effect

There was no evidence that escitalopram was associated with a smaller rate of adverse events than bupropion (OR 0.77, 95% CI 0.55 to 1.07, p = 0.12; 3 studies, 822 participants) (Analysis 10.2).

Total number of patients experiencing a specific side effect (only figures for statistically significant differences were reported in the text)

a) Agitation/Anxiety: No difference was found between escitalopram and bupropion in terms of number of participants experiencing agitation/anxiety (Analysis 11.2).

b) Constipation: There was evidence that escitalopram was associated with a lower rate of participants experiencing constipation than bupropion (OR 0.32, 95% CI 0.15 to 0.69, p = 0.004; 2 studies, 557 participants (Analysis 12.2).

c) Diarrhoea: No difference was found between escitalopram and bupropion in terms of number of participants experiencing diarrhoea (Analysis 13.2).

d) Dry mouth: There was evidence that escitalopram was associated with a lower rate of participants experiencing dry mouth than bupropion (OR 0.58, 95% CI 0.39 to 0.87, p = 0.007; 3 studies, 822 participants) (Analysis 14.2).

e) Hypotension: No data reported.

f) Insomnia: There was evidence that escitalopram was associated with a lower rate of participants experiencing insomnia than bupropion (OR 0.55, 95% CI 0.33 to 0.92, p = 0.02; 3 studies, 822 participants) (Analysis 16.2).

g) Nausea: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing nausea than bupropion (Analysis 17.2).

h) Urination problem: No data reported.

i) Sleepiness/drowsiness: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing sleepiness than bupropion (Analysis 18.2).

j) Vomiting: No data reported.

k) Deaths, suicide and suicidality: Two patients developed suicidal ideation/tendency (both in the escitalopram group), however this difference was not statistically significant (Analysis 31.1). Neither deaths, nor completed or attempted suicides were reported.

l) Other adverse events: There was evidence that escitalopram was associated with a higher rate of participants experiencing fatigue (OR 3.48, 95%CI 1.77 to 6.84, p = 0.0003; 2 studies, 557 participants) (Analysis 21.2) and yawning (OR 7.71, 95%CI 1.75 to 34.05, p = 0.007; 2 studies, 557 participants) (Analysis 30.2) than bupropion. Although not statistically significant, there was some evidence that irritability was less frequent in patients randomised to escitalopram than in patients allocated to bupropion (OR 0.26, 95% CI 0.06 to 1.04, p = 0.06; 2 trials, 557 participants). No statistically significant differences were found for dizziness (Analysis 20.2), headache (Analysis 23.2), or pain (Analysis 28.1, Analysis 28.2, Analysis 28.3, Analysis 28.4).

B. ESCITALOPRAM versus DULOXETINE

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than duloxetine in terms of response to treatment in the acute phase (OR 0.72, 95% CI 0.43 to 1.20, p = 0.21; 3 studies, 1120 participants) (see Figure 9).

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

c) Follow-up response (16 to 24 weeks): There was no evidence that escitalopram was more or less efficacious than duloxetine in terms of response to treatment at 24 weeks (OR 0.72, 95% CI 0.42 to 1.25, p = 0.25; 1 study, 295 participants) (Analysis 3.2).

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than duloxetine in terms of remission of depressive symptoms during the acute phase treatment (OR 0.90, 95% CI 0.62 to 1.29, p = 0.56; 3 studies, 1120 participants) (see Figure 10).

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

c) Follow-up response (16 to 24 weeks): There was no evidence that escitalopram was more or less efficacious than duloxetine in terms of remission of depressive symptoms at 24 weeks (OR 0.72, 95% CI 0.45 to 1.16, p = 0.18; 1 study, 295 participants) (Analysis 5.1).

a) Acute phase treatment: between 6 and 12 weeks: There was no evidence that escitalopram was more or less efficacious than duloxetine in reduction of depressive symptoms (SMD −0.10, 95% CI −0.30 to 0.09, p = 0.28; 3 studies, 1096 participants) (see Figure 11).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: One study (Wade 2007) used the SF-36 as a measure of general health status. Ratings from eight subscales were reported and no statistically significant differences between escitalopram and duloxetine were found (data not shown here but available from authors).

- **a.** There was a statistically significant difference with fewer patients allocated to escitalopram withdrawing from study than duloxetine for discontinuation due to any cause (OR 0.62, 95% CI 0.38 to 0.99, p = 0.05; 3 studies, 1120 participants) (see Figure 12).
- **b.** No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 0.95, 95% CI 0.21 to 4.25, p = 0.95; 3 studies, 1120 participants) (see Figure 13)
- **c.** No statistically significant difference was found in terms of discontinuation due to side effects (OR 0.49, 95% CI 0.18 to 1.29, p = 0.15; 3 studies, 1120 participants) (see Figure 14)

7) TOLERABILITY: Total number of patients experiencing at least one side effect.

No statistically significant difference was found in terms of rate of adverse events (OR 0.96, 95% CI 0.67 to 1.38, p = 0.82; 3 studies, 1111 participants) (Analysis 10.2).

Total number of patients experiencing a specific side effect (only figures for statistically significant differences were reported in the text)

a) Agitation/Anxiety: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing agitation/anxiety than duloxetine (Analysis 11.2).

b) Constipation: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing constipation than duloxetine (Analysis 12.2).

c) Diarrhoea: No difference was found between escitalopram and duloxetine in terms of number of participants experiencing diarrhoea (Analysis 13.2).

d) Dry mouth: There was evidence that escitalopram was associated with a lower rate of participants experiencing dry mouth than duloxetine (OR 0.55, 95% CI 0.39 to 0.79, p = 0.001; 3 trials, 1111 participants) (Analysis 14.2).

e) Hypotension: No data reported.

f) Insomnia: Even though not statistically significant, there was some evidence that insomnia was less frequent in patients treated with escitalopram than in patients randomised to duloxetine (OR 0.58, 95% CI 0.33 to 1.02, p = 0.06; 3 trials, 1111 participants) (Analysis 16.2).

g) Nausea: There was evidence that escitalopram was associated with a lower rate of participants experiencing nausea than duloxetine (OR 0.56, 95% CI 0.42 to 0.75, p = 0.0001; 3 trials, 1111 participants) (Analysis 17.2).

h) Urination problem: No data reported.

i) Sleepiness/drowsiness: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing sleepiness than duloxetine (Analysis 18.2).

j) Vomiting: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing vomiting than duloxetine (Analysis 19.2).

k) Deaths, suicide and suicidality: Overall two patients died, one in the escitalopram group and one in the duloxetine group (this patient committed suicide), and these differences were not statistically significant (Analysis 31.3, Analysis 31.4). No data about attempted suicide or suicidal tendency/ideation were reported.

l) Other adverse events: Escitalopram was associated with a lower rate of participants experiencing dizziness than duloxetine (OR 0.59, 95%CI 0.39 to 0.90, p = 0.01; 3 trials, 1111 participants). (Analysis 20.2). Though not statistically significant, there was some evidence that irritability was less frequent in patients randomised to escitalopram than in patients treated with duloxetine (OR 0.39, 95% CI 0.15 to 1.01, p = 0.05; 1 trials, 547 participants. No statistically significant differences were found for fatigue (Analysis 21.2), flu syndrome (Analysis 22.2), headache (Analysis 23.2), decreased libido (Analysis 27.2), pain (Analysis 28.2), increased sweating (Analysis 29.2) and yawning (Analysis 30.2).

C. ESCITALOPRAM versus VENLAFAXINE

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than venlafaxine in terms of response to treatment in the acute phase (OR 0.86, 95% CI 0.53 to 1.39, p = 0.53; 2 studies, 495 participants) (see Figure 9).

b) Early response (1 to 4 weeks): Only one trial reported data on the early phase of treatment and the difference was not statistically significant (OR 0.85, 95% CI 0.47 to 1.55, p = 0.60; 1 study, 293 participants) (Analysis 2.2).

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

a) Acute phase treatment (6 to 12 weeks): There was no evidence that escitalopram was more or less efficacious than venlafaxine in terms of remission of depressive symptoms during the acute phase treatment (OR 0.91, 95% CI 0.63 to 1.33, p = 0.64; 2 studies, 495 participants) (see Figure 10).

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

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

a) Acute phase treatment: between 6 and 12 weeks: There was no evidence that escitalopram was more or less efficacious than venlafaxine in reduction of depressive symptoms (SMD −0.07, 95% CI −0.38 to 0.25, p = 0.68; 5 studies, 283 participants) (see Figure 11).

3) to 5) EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services: No data available.

- **a.** No statistically significant difference was found in terms of discontinuation due to any cause (OR 0.90, 95% CI 0.58 to 1.39, p = 0.62; 2 studies, 495 participants) (see Figure 12).
- **b.** No statistically significant difference was found in terms of discontinuation due to inefficacy (OR 9.06, 95% CI 0.48 to 169.85, p = 0.14; 1 study, 293 participants) (see Figure 13).
- **c.** There was no evidence that escitalopram was statistically significantly better than venlafaxine in terms of discontinuation due to side effects (OR 0.41, 95% CI 0.14 to 1.17, p = 0.09; 2 studies, 495 participants) (see Figure 14).

7) TOLERABILITY: Total number of patients experiencing at least one side effect

There was no evidence that escitalopram was associated with a smaller rate of adverse events than venlafaxine (OR 0.58, 95% CI 0.28 to 1.23, p = 0.16; 2 studies, 487 participants) (Analysis 10.2).

Total number of patients experiencing a specific side effect (only figures for statistically significant differences were reported in the text)

a) Agitation/Anxiety: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing agitation/anxiety than venlafaxine (Analysis 11.2).

b) Constipation: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing constipation than venlafaxine (Analysis 12.2).

c) Diarrhoea: No difference was found between escitalopram and venlafaxine in terms of number of participants experiencing diarrhoea (Analysis 13.2).

d) Dry mouth: There was no evidence that escitalopram was associated with a higher or lower rate of participants experiencing dry mouth than venlafaxine (Analysis 14.2).

e) Hypotension: No data reported.

f) Insomnia: No difference was found between escitalopram and venlafaxine in terms of number of participants experiencing insomnia (Analysis 16.2).

g) Nausea: There was evidence that escitalopram was associated with a lower rate of participants experiencing nausea than venlafaxine (OR 0.37, 95% CI 0.14 to 0.99, p = 0.05; 2 trials, 487 participants) (Analysis 17.2).

h) Urination problem: No data reported.

i) Sleepiness/drowsiness: No difference was found between escitalopram and venlafaxine in terms of number of participants experiencing sleepiness (Analysis 18.2).

j) Vomiting: No data reported.

k) Deaths, suicide and suicidality: One patient developed suicidal ideation/tendency (in the escitalopram group) (Analysis 31.1) and two patients attempted suicide (both randomised to escitalopram) (Analysis 31.2). One patient died in the venlafaxine group (Analysis 31.4) but no completed suicide was reported in both the comparisons. None of these differences were statistically significant.

l) Other adverse events: Escitalopram was associated with a lower rate of participants experiencing increased sweating than venlafaxine (OR 0.45, 95%CI 0.23 to 0.87, p = 0.02; 2 trials, 487 participants (Analysis 29.2). No statistically significant differences were found for dizziness (Analysis 20.2), fatigue (Analysis 21.2), headache (Analysis 23.2), impotence (Analysis 24.2), lethargy/sedation (Analysis 26.2), decreased libido (Analysis 27.2) and pain (Analysis 28.1, Analysis 28.2).

SUBGROUP ANALYSES

1) Escitalopram dosing: All studies used escitalopram within the standard therapeutic range (10 to 20 mg/day), with the exception of only one unpublished study (SCT-MD-35) where escitalopram dose was set at 4 mg/day. Therefore, it was not meaningful to carry out this pre-planned sub-group analysis.

2) Comparator dosing: All comparator doses were within the therapeutic range, with the exception of two studies (SCT-MD-35; Yevtushenko 2007). Due to the small number of trials without the therapeutic range, it was not considered meaningful to carry out this pre-planned subgroup analysis.

3) Depression severity: All studies reported a mean baseline score corresponding to moderate to severe major depression, with the exception of three studies where the mean baseline score corresponded to a mild major depression (Montgomery 2004; Nierenberg 2007; SCT-MD-09). Therefore, it was not meaningful to carry out this pre-planned sub-group analysis.

4) Treatment settings: Only one study selectively recruited patients in general practice (Lepola 2003) and no studies enrolled only inpatients, therefore it was not considered meaningful to carry out this pre-planned subgroup analysis.

5) Elderly patients: As only one study specifically recruited elderly patients (Kasper 2005), it was not meaningful to carry out this pre-planned subgroup analysis.

FUNNEL PLOT ANALYSIS: As stated in the protocol, analyses were carried out as head-to head 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: Although technically possible to carry out these sensitivity analyses, they were not performed, because they would not have contributed useful information due to the small number of studies (only four trials) reporting clear details on concealment of random allocation (Baldwin 2006; Boulenger 2006; Wade 2007; Colonna 2005).

2) Excluding trials whose dropout rate was greater than 20%: Referring to other SSRIs, a dropout rate greater than 20% was found for two studies comparing escitalopram with citalopram (Burke 2002; SCT-MD-02), one with fluoxetine (Kennedy 2005) and one with paroxetine (Boulenger 2006). Among newer antidepressants, a dropout rate greater than 20% was found for all the three studies comparing escitalopram with bupropion (Clayton (AK130926); Clayton (AK130927); SCT-MD-35), two with duloxetine (Nierenberg 2007; Wade 2007) and one with venlafaxine (Bielski 2004). Three studies had only one arm reporting a dropout rate greater than 20% (Colonna 2005; Kasper 2005; Khan 2007). Therefore, sensitivity analyses were carried out only for the comparisons between (i) escitalopram and citalopram, and (ii) escitalopram and fluoxetine.

a) escitalopram vs citalopram: Results from the sensitivity analyses were still statistically significant in favour of escitalopram, not only when trials whose dropout rate was greater than 20% in both arms were excluded (OR 0.56, 95% CI 0.40 to 0.79, p = 0.0009; 4 studies, 1187 participants) but also when trials whose dropout rate was greater than 20% in only one arm were additionally excluded (OR 0.49, 95% CI 0.34 to 0.72, p = 0.0002; 3 studies, 830 participants).

b) escitalopram vs fluoxetine: Results from the sensitivity analyses were still not statistically significant when trials whose dropout rate was greater than 20% in both arms were excluded (OR 0.80, 95% CI 0.56 to 1.13, p = 0.20; 2 studies, 578 participants).

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

a) Imputed response rate: Excluding trials for which the response rate had to be calculated based on the imputation method, results for all comparisons did not materially change.

b) Imputed remission rate: Excluding trials for which the remission rate had to be calculated based on the imputation method, results for all comparisons did not materially change.

c) Borrowed SDs: Excluding trials for which the SD had to be borrowed from other trials, the two previously statistically significant results (namely, escitalopram versus citalopram and escitalopram versus fluoxetine) became no more statistically significant. The remaining outcomes did not materially change.

5) Examination of "wish bias" and exclusion of studies funded by the pharmaceutical company marketing escitalopram: These pre-planned sensitivity analyses were not carried out because there were insufficient trials run by manufacturers other than the one marketing escitalopram to allow meaningful formal assessment. In almost all the included studies (19 out of 22) escitalopram was the investigational drug, with the exception of two studies carried out by the bupropion manufacturer (Clayton (AK130926); Clayton (AK130927)), one by the duloxetine manufacturer (Nierenberg 2007) where escitalopram was used as reference compound.

DISCUSSION

Summary of main results

Twenty two trials were included in this review. Some statistically significant differences favouring escitalopram over other antidepressants for the acute phase treatment of major depression were found in terms of efficacy (citalopram and fluoxetine) and acceptability (duloxetine). 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, patients' and their carers' attitudes to treatment, their ability to return to work and resume normal social functioning, were not reported in the included studies. Almost one third of trials used citalopram as the comparator and only a small number of trials per comparison were found for most of the remaining antidepressants (with the exception of fluoxetine). This limits the power of the review to detect moderate, but clinically meaningful differences between the drugs. The dataset of the present review collected insufficient randomised evidence to detect a difference in early response to treatment (after two weeks of treatment). Looking at the data reported in the trials included in this systematic review,

the question on comparative efficacy of early onset response has yet to be proven and remains a matter of ongoing debate (Gourion 2008).

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 (Kupfer 2002), however, in the present review we focused only on the comparison between escitalopram and other active treatments. Retrieved randomised evidence compared escitalopram with a small selection of possible comparator antidepressants and no randomised trials comparing escitalopram with fluvoxamine (amongst SSRIs), or with mirtazapine, reboxetine, milnacipran or hypericum (amongst the newest antidepressants), or with any of the first generation antidepressants (such as TCAs or MAOIs) 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. As in all systematic reviews and meta-analyses, in the present study the main concern is about the amount of the included information. The more information that is pooled together, the more precise and accurate is the estimate (Higgins 2005). We are realistically aware that a possibly significant piece of information has not been published and thus is not contributing to the true treatment estimate we were seeking. Although we did our very best to retrieve as many 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. We are also aware of the possibility that a number of further randomised controlled trials comparing escitalopram with other antidepressant drugs are currently being conducted and will be included in future updates of the review.

Quality of the evidence

In this review the mean sample size was bigger than mean sample size of antidepressant studies included in a similar systematic review comparing fluoxetine versus other antidepressants (Cipriani 2005). Escitalopram is a relatively new compound and the quality of trials in psychiatry may have improved in the last years. Notwithstanding the increased sample size, the great majority of trials still do not report adequate information about randomisation and allocation concealment. The reporting of the outcomes in the included studies was often unclear or incomplete and the figures used for the analyses not immediately understandable. All antidepressant studies included in the review were very similar in design and conduct, and the scant information about randomisation and allocation concealment may be matter of reporting in the text than real defects in study design. However, sometimes there were some discrepancies between published reports and unpublished data available on the websites of the pharmaceutical industries. Dealing with summary statistics, the quality of information is important. Meta-analyses of poor quality studies may be seriously misleading, because the bias associated with defects in the conduct of primary studies (randomised trials) can seriously affect overall estimates of intervention. Systematic reviewers (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).

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Potential biases in the review process

There is unanimous evidence of presence of sponsorship bias in medicine and long-standing concern exists about the potential influence of financial interests on medical literature (Djulbegovic 2000). In the field of antidepressant trials sponsorship can play an important role (Bekelman 2003). In this review the great majority of the trials were sponsored by the escitalopram manufacturer. Because nearly all the trials were sponsored by the drug company marketing escitalopram, it was not possible to formally examine the potential influence of sponsorship bias in sensitivity analyses. For this reason, the potential for an overestimation of the effect size favouring escitalopram need be considered. Limitations of the primary trials and potential confounders may affect the validity of the findings. Readers cannot fully appreciate a study's meaning without acknowledging the subtle biases in design and interpretation that may arise when a sponsor stands to gain from the report (Schwartz 2008). Such associations should be made clear to let anyone judge the relevance of findings.

To clinically assess comparative treatment effectiveness, in this study we used both dichotomous and continuous outcomes (the number of patients who responded and the mean change between baseline and endpoint on standardised rating scales for depressive symptoms, respectively). It has been claimed that a very small difference in symptom score can translate into a very large difference in the proportion of patients who responded (Moncrieff 2005), however in this review we found that a statistically significant difference in symptom score did not translate into a significant difference in terms of dichotomous outcome. We used an imputation method to impute missing SDs. As reported in the result section, a sensitivity analysis excluding trials for which the SD had to be borrowed was pre-planned and carried out, and the two previously statistically significant results became no more statistically significant. For the fluoxetine comparison, this might be due to the imputation method which could have allowed us to use possibly narrower SDs; by contrast, for the citalopram versus escitalopram studies the difference might be due to the reduction of the overall sample size and, therefore, to the consequent loss of statistical power. However, even though no more statistically significant, the ORs in the sensitivity analysis were consistent with the primary overall analysis. A substantial limitation of some trials was the high rate of patients lost on follow-up (more than 30%). High withdrawal rates reduce the reliability of the assessment of other outcomes. A further limitation of this analysis is that by making multiple comparisons we might have committed a type 1 error, that is, reporting a spurious association. Therefore, results should be interpreted with caution.

Agreements and disagreements with other studies or reviews

In terms of side effect profile, different tolerability profiles for different antidepressants were found. This is an important issue from a clinical point of view and results from this review are consistent with previous findings (Cipriani 2005; Hansen 2005). However, a full description of tolerability profile of drugs cannot rely solely on randomised evidence (Etminan 2005). Furthermore, adverse effects were inconsistently reported in the studies in the present review, thus hampering cross-study comparisons. Standardisation in the reporting of adverse effects is needed, and patients' subjective experience of medication should be given more consideration. The issue about tolerability is clinically important because during the evidence-based decision-making process, clinicians should take into

consideration and inform patients of different side effect profiles among antidepressants. However, it has been shown that randomised controlled trials might not be the most effective tool to identify possible causal relationship between antidepressants and even severe adverse events (De Abajo 2008). This is true for class-related adverse event, but might also be true for each specific compound. As it happens for the second generation antipsychotics (Kumra 2008), newer antidepressants need more reliable and longer-term studies before knowing the real impact and burden on treated patients in terms of tolerability.

Dosage is another compelling issue when dealing with pharmacological treatments (Barbui 2004). In this review almost all studies used treatments within the therapeutic range. Half the studies used a fixed-dose regimen design and the remaining eleven a flexibledose one. Among the included studies there was no evidence of imbalance in terms of dose design or disease severity favouring the investigational drugs.

AUTHORS' CONCLUSIONS

Implications for practice

Escitalopram appears to be suitable as first-line antidepressant treatment for moderate to severe major depression. It has been compared with only a few other antidepressants and so we are unable to say whether it is better, worse or the same as many of the other drugs used in practice. As for all other new investigational compounds, the potential for overestimation of treatment effect due to sponsorship bias should be borne in mind. Results reported for comparative efficacy have therefore to be viewed with caution.

Cost effectiveness evaluation of pharmacological treatments is extremely important for health policy purposes. Health economic models have been constructed to assess the cost-utility of antidepressant treatments (Sobocki 2008) and new modelling has been developed to provide methodological benefits in depicting evolution of major depressive disorder, as well (Le Lay 2006). By contrast, even though NICE guidelines suggested to prescribe antidepressant with generic formulation (NICE 2007), physicians infrequently discuss medication cost and acquisition issues when prescribing new medications (Tarn 2006). Some antidepressants have a lower acquisition cost and these are the non-patented drugs. Nowadays only two antidepressants, escitalopram and duloxetine, are still on patent in the US and in Europe. In this analysis we did not perform a full economic analysis. To simply rely on lower cost is not justified by the literature, because the acquisition cost may differ country by country and because several other costs associated with the use of antidepressants should be considered (Le Lay 2006). However, acquisition cost of antidepressants may play a important role in impacting on the economic burden of drug prescription for such a common mental health disorder as depression, most of all in developing countries (Patel 2007).

Implications for research

Future studies should focus to a greater extent on outcomes of clear relevance to patients and clinicians, in particular, patients' and carers' attitudes to treatment, their ability to return to

work and resume normal social functioning. Cost-effectiveness information is also needed in the field of antidepressant trials. Recognising the importance of addressing cost and acquisition issues with patients, appropriate economic analysis independent from pharmaceutical industry considering both costs and clinical outcomes should be carried out in the field of antidepressant trials, to improve physician knowledge about helping patients achieve affordable medication regimens.

The main methodological limitation of standard systematic reviews is that they can rely only on evidence from direct comparisons. However, given the wide spectrum of available comparisons for the treatment of major depression, the use of the methodology of multiple treatments meta-analysis (MTM) may help overcome this limitation (Lumley 2002; Lu 2006; Salanti 2008). MTM (also known as *network meta-analysis*) is a statistical method that enables to integrate data from direct comparisons (when treatments are compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are against a common comparator treatment) involving diverse regimens, and to assess the strength and consistency of the evidence. Many new drugs have been introduced for the treatment of depressive disorder over the last twenty years, many of which are structurally related and share similar putative mechanisms of action. It is unclear to what extent these agents vary in terms of efficacy and tolerability and some of the more recently introduced drugs (e.g. escitalopram) appear to be chemically similar to existing drugs with expiring patents rather than genuine advances in treatment. Some systematic reviews have found inconsistent differences in efficacy between second-generation antidepressants both within and between classes. MTM has already been used in other fields of medicine (Psaty 2003; Elliott 2007) and the review of a MTM comparing a group of antidepressants has been recently published (Cipriani 2009). MTM may provide a clinically useful summary of the results that can be used to guide treatment decisions.

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- No sources of support supplied

CHARACTERISTICS OF STUDIES

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

Alexopoulos 2004

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a minimum score of 22 on Montgomery-Asberg Depression Ration Scale. Age range: 18-65 years.
Interventions	Escitalopram: 136 participants. Sertraline: 138 participants. Escitalopram dose range: 10-20 mg/day. Sertraline dose range: 50-200 mg/day.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Ration Scale. Secondary Outcomes: Hamilton Depression Rating Scale - 24 Item, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	Only unpublished data. This study was funded by escitalopram manufacturer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done.
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Unclear	No information provided.
Incomplete outcome data addressed? All outcomes	Yes	Quote: "ITT population, which included patients who had at least one post-baseline assessment of MADRS"
Free of selective reporting?	Yes	

Baldwin 2006

Methods	Eight-week, double-blind, randomised, multicentre study . Patients demonstrating evidence of clinical improvement (CGI-I <= 2) at week 8 entered a 19-week, double-blind continuation period. At the end of the continuation period, patients entered a 1- or 2-week down-tapering period randomly scheduled to start between weeks 28 and 31. All patients received placebo during week 32 and no study product thereafter
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a total score on Montgomery-Asberg Depression Rating Scale (MADRS) between 22 and 40. Age range: 18 years or older. Exclusion criteria: another Axis I disorder within the previous 6 months, learning disability or other cognitive disorder, serious risk of suicide (such as when the patient was rated >= 5 on MADRS item 10), previous failure to respond or hypersensitivity to citalopram and/or paroxetine, a history of severe drug allergy or hypersensitivity, a history of lactose intolerance, use of a psychoactive drug within the past 2 weeks (5 weeks for fluoxetine) , use of triptans, oral anticoagulants, sildenafil citrate, cimetidine, type 1 c anti-arrhythmics, cardiac glycosides, narcotic analgesic or an investigational drug within the past 3 months, formal psychotherapy
Interventions	Escitalopram: 166 participants. Paroxetine: 159 participants. Escitalopram dose range: 10-20 mg/day. Paroxetine dose range: 20-40 mg/day. Benzodiazepines were allowed if the dose had been stable for the previous 6 months and remained fixed during the study

Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcomes: Hamilton Rating Scale for Depression - 24 Item, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "computer-generated randomization list"
Allocation concealment?	Yes	Quote: "sealed opaque envelopes"
Blinding? All outcomes	Yes	Quote: "all study personnel and participants were blinded to treatment assignment for the duration of the study"
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Missing information on standard deviation
Free of other bias?	Yes	

Bielski 2004

Methods	Eight-week, double-blind, randomised, multicentre study, followed by a two week, double-blind, down-titration period
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a minimum score of 20 on Hamilton Depression Rating Scale. Age range: 18-65 years. Exclusion criteria: abnormal results of physical examinations, laboratory tests and electrocardiograms (ECG), pregnancy, lactation, any Axis I disorder other than major depressive disorder, substance abuse or dependence within the past 6 months, risk of suicide, any clinically significant medical illness that had not been stable for at least 1 year, use of a depot neuroleptic within the past 6 months, use of any neuroleptic, antidepressant or anxiolytic medication within the past 2 weeks (5 weeks for fluoxetine), previous treatment with either escitalopram or venlafaxine, previous failure to respond to adequate trials of 2 or more antidepressants, concomitant use of any psychoactive drug (or any drug with a psychotropic component)
Interventions	Escitalopram: 101 participants. Venlafaxine XR: 101 participants. Escitalopram dose: 20 mg/day. Venlafaxine XR dose: 225 mg/day. Zolpidem or Zaleplon were allowed for sleep.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale Secondary Outcomes: Hamilton Depression Rating Scale - 24 Item, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	A greater proportion of patients randomly assigned to receive escitalopram were female (69,4%) compared with the venlafaxine XR group (47,0%; p<,01). This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "randomly assigned". Probably done.

Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Unclear	No information provided
Incomplete outcome data addressed? All outcomes	Yes	Quote: “ITT population, that is those who had received at least 1 dose of double-blind study medication and had at least one post-baseline MADRS assessment”
Free of selective reporting?	Yes	

Boulenger 2006

Methods	24-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a minimum score of 30 on Montgomery-Asberg Depression Rating Scale (MADRS) . Age range: 18-75 years. Exclusion criteria: bipolar disorder, psychotic disorder or features, obsessive-compulsive disorder, current eating disorders, mental retardation, any pervasive developmental disorder or cognitive disorder, or alcohol or drug abuse-related disorders within the past 12 months, a serious risk of suicide (a minimum score of 5 on item 10 of the MADRS) , concomitant behaviour therapy or systematic psychotherapy, pregnancy or breastfeeding, a history of lactose intolerance, a history of hypersensitivity or non-response to citalopram or escitalopram or duloxetine or with increased intra-ocular pressure, risk of acute narrow-angle glaucoma, use within the past 2 weeks of MAOI or RIMA, SSRIs (fluoxetine within 5 weeks), SNRIs, tricyclic antidepressants, tryptophan, psychoactive herbal remedies, any drug used for augmentation of antidepressant action or any other antidepressant drugs, oral antipsychotics and anti-manic drugs, dopamine antagonists, anxiolytics, any anticonvulsant drug, serotoninergic agonists, narcotic analgesics, cardiac glycosides, type 1c anti-arrythmics, oral anticoagulants, cimetidine, potent inhibitors of CYP2C19, CYP1A2, or medicinal products with a narrow therapeutic index predominantly metabolised by CYP2D6, use of ECT within the past 6 months
Interventions	Escitalopram: 232 participants. Paroxetine: 227 participants. Escitalopram dose: 20 mg/day. Paroxetine dose: 40 mg/day. Zolpidem, zolpiclone or zaleplon used episodically for insomnia were allowed
Outcomes	Primary Outcome: Change from baseline to week 24 in Montgomery-Asberg Depression Rating Scale Secondary Outcomes: Hamilton Depression Scale - 24 and 17 item, Hamilton Anxiety Scale, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer

Risk of bias

Item	**Authors’ judgement**	**Description**
Adequate sequence generation?	Yes	Quote: “Patients …. were assigned to 24 weeks of double-blind treatment in a 1:1 ratio … according to a computer-generated randomisation list.”
Allocation concealment?	Yes	Quote: “The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available in blocks of 4.”
Blinding? All outcomes	Yes	Quote: “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 addressed? All outcomes	Yes	The prospectively defined primary end-point was the adjusted mean change in MADRS total score from baseline to Week 24, based on the intent-to-treat set (ITT) and using last-observation-carried-forward (LOCF) analysis
Free of selective reporting?	Yes	

Burke 2002

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 22 on Montgomery-Asberg Depression Rating Scale (MADRS) and a minimum score of 2 on Item 1 of Hamilton Depression Rating Scale. Age range: 18-65 years. Exclusion criteria: any DSM-IV Axis I disorder other than major depression, any personality disorder, a history of substance abuse, a suicide attempt within the past year or evidence of active suicidal ideation (as indicated by a score of at least 5 on item 10 of the MADRS), pregnancy, lactation, women of childbearing potential if they didn’t agree to use a medically acceptable method of contraception, concomitant psychotropic medication
Interventions	Escitalopram: 252. Citalopram: 127. Escitalopram dose range: 10-20 mg/day. Citalopram dose: 40 mg/day. Zolpidem for insomnia was allowed (no more than 3 times per week)
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcomes: Hamilton Depression Rating Scale, HAMD Depressed Mood Item, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	This study was funded by escitalopram manufacturer

Risk of bias

Item	**Authors’ judgement**	**Description**
Adequate sequence generation?	Yes	Quote: “randomly assigned”. Probably done
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Unclear	No clear information provided
Incomplete outcome data addressed? All outcomes	Yes	Quote: “Last-observation-carried-forward approach that included patients who had received at least 1 dose of double-blind study medication and had at least one post-baseline MADRS assessment”
Free of selective reporting?	No	Only graphs and a few side effects reported

Clayton (AK130926)

Methods	Eight-week, double-blind, double-dummy, randomised, multicentre study

Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 19 on a 17-item Hamilton Rating Scale for Depression, with normal orgasm function, engaging in sexual activity leading to orgasm at least once every 2 weeks. Age range: 18 years or older. Exclusion criteria: any sexual dysfunction except sexual desire disorder related to depression, history of anorexia nervosa, bulimia, seizure disorder, brain injury, diagnosis of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder or acute stress disorder within the past 12 months, diagnosis of bipolar I or II disorder, schizophrenia or other psychotic disorders, history of attempted suicide within the past 6 months, use of medications that might affect sexual functioning
Interventions	Escitalopram: 138. Bupropion XR: 141. Escitalopram dose range: 10-20 mg/day. Bupropion XR dose range: 300-450 mg/day.
Outcomes	Primary Outcome: Percentage of subjects with orgasm dysfunction and change from baseline to week 8 in 17-item Hamilton Depression Rating Scale. Secondary Outcomes: Percentage of subjects with worsened sexual function, percentage of subjects satisfied with their sexual functioning, 17-item Hamilton Depression Scale
Notes	This study was funded by burpopion manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomised". Probably done
Allocation concealment?	Unclear	No information reported
Blinding? All outcomes	Unclear	No information reported
Incomplete outcome data addressed? All outcomes	No	ITT population defined as all randomised patients who took at least 1 dose of study medication, had no orgasm dysfunction reported from the sexual functioning assessment at rendomization, had a HAM-D assessment completed at randomization and provided at least 1 post-randomization HAMD-17 and orgasm function assessment
Free of selective reporting?	Yes	

Clayton (AK130927)

Methods	Eight-week, double-blind, double-dummy, randomised, multicentre study
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 19 on a 17-item Hamilton Rating Scale for Depression, with normal orgasm function, engaging in sexual activity leading to orgasm at least once every 2 weeks. Age range: 18 years or older. Exclusion criteria: any sexual dysfunction except sexual desire disorder related to depression, history of anorexia nervosa, bulimia, seizure disorder, brain injury, diagnosis of panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder or acute stress disorder within the past 12 months, diagnosis of bipolar I or II disorder, schizophrenia or other psychotic disorders, history of attempted suicide within the past 6 months, use of medications that might affect sexual functioning
Interventions	Escitalopram: 149. Bupropion XR: 138. Escitalopram dose range: 10-20 mg/day. Bupropion XR dose range: 300-450 mg/day.
Outcomes	Primary Outcome: Percentage of subjects with orgasm dysfunction and change from base'line to week 8 in 17-item Hamilton Depression Rating Scale.

	Secondary Outcomes: Percentage of subjects with worsened sexual function, percentage of subjects satisfied with their sexual functioning, 17-item Hamilton Depression Scale
Notes	This study was funded by burpopion manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomised". Probably done
Allocation concealment?	Unclear	No information reported
Blinding? All outcomes	Unclear	No information reported
Incomplete outcome data addressed? All outcomes	No	ITT population defined as all randomised patients who took at least 1 dose of study medication, had no orgasm dysfunction reported from the sexual functioning assessment at rendomization, had a HAM-D assessment completed at randomization and provided at least 1 post-randomization HAMD-17 and orgasm function assessment
Free of selective reporting?	Yes	

Colonna 2005

Methods	24-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a total score between 22 and 40 on Montgomery-Asberg Depression Rating Scale (MADRS). Age range: 18-65 years. Exclusion criteria: other serious illnesses on the basis of medical history and the screening results of a physical examination, electrocardiogram (ECG) and clinical laboratory tests, pregnancy, breast-feeding, non adequate contraception at time of screening, mania or any bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, eating disorders, mental retardation or any pervasive developmental or cognitive disorder, MADRS score >= 5 on item 10, concomitant treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics, barbiturates, chloral hydrate, 5-HT receptor agonists, electroconvulsive treatment, behaviour therapy or psychotherapy, use of any investigational drug within the past 30 days, history of schizophrenia, psychotic disorder or drug abuse, history of severe drug allergy or hypersensitivity (including to citalopram), a lack of response to more than one antidepressant treatment (including citalopram) during the present depressive episode
Interventions	Escitalopram: 175 participants. Citalopram: 182 participants. Escitalopram dose: 10 mg/day. Citalopram dose: 20 mg/day. Benzodiazepines in low doses for insomnia were allowed.
Outcomes	Primary Outcome: Change from baseline in the mean of the Montgomery-Asberg Depression Rating Scale during the 24 weeks. Secondary Outcomes: MADRS single items, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "computer-generated randomization list"

Allocation concealment?	Yes	Quote: “sealed opaque envelopes”
Blinding? All outcomes	Yes	Quote: “all study personnel and participants were blinded”
Incomplete outcome data addressed? All outcomes	Yes	Quote: “ITT population included all randomised patients who took at least one dose of double-blind study product and who had at least one valid post-baseline MADRS assessment.”
Free of selective reporting?	No	Missing standard deviations.
Free of other bias?	Yes	

Kasper 2005

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	In- and out-patients meeting DSM-IV criteria for Major Depression Disorder, having a total score between 22 and 40 on Montogmery-Asberg Depression Rating Scale (MADRS) and a minimum score of 22 on Mini Mental State Examination (MMSE). Age range: 65 years or older. Criteria exclusion: DSM-IV criteria for mania or any bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, eating disorders, mental retardation or pervasive developmental or cognitive disorder, a MADRS score >= 5 on Item 10, concomitant treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, antiepileptics, barbiturates, chloral hydrate, antiparkinsonian drugs, diuretics, 5-HT receptor agonists, lithium, sodium valproate, carbamazepine, electroconvulsive treatment, behaviour therapy or psychotherapy, use of an investigational drug within the past 30 days, a history of schizophrenia or psychotic disorder or drug abuse, a history of severe allergy or hypersensitivity (including to citalopram), a lack of response to more than one antidepressant treatment (including citalopram) during the present depressive episode
Interventions	Escitalopram: 174 participants. Fluoxetine: 164 participants. Escitalopram dose: 10 mg/day. Fluoxetine dose: 20 mg/day. Oxazepam (maximum 30 mg/day), temazepam (maximum 10 mg/day), zopiclone (maximum 3,75 mg/day), zolpidem (maximum 5 mg/day) were allowed
Outcomes	Change from baseline to final assessment in Montogmery-Asberg Depression Rating Scale
Notes	Settings: both general practice and specialist. Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer

Risk of bias

Item	**Authors’ judgement**	**Description**
Adequate sequence generation?	Yes	Quote: “randomized”. Probably done
Allocation concealment?	Unclear	No information provided
Incomplete outcome data addressed? All outcomes	Yes	Quote: “ITT including all randomized patients who took at least one dose of double-blind study medication and who had at least one post-baseline assessment of the MADRS total score”

Kennedy 2005

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 22 on Montgomery-Asberg Depression Rating Scale. Age range: 18-80 years.
Interventions	Escitalopram: 102 participants. Fluoxetine: 103 participants. Escitalopram dose range: 10-20 mg/day. Fluoxetine: 20-40 mg/day.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcomes: Hamilton Depression Rating Scale, Hamilton Anxiety Scale, Clinical Global Impression - Improvement, Clinical Global Impression - Severity, Center of Epidemiologic Studies - Depression Scale, Quality of Life Scale
Notes	Only unpuplished data. This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Blinding? All outcomes	Unclear	Quote: "double-blind".
Incomplete outcome data addressed? All outcomes	Yes	Quote: ITT analysis ("all patients with at least one post-baseline assessment of MADRS")

Khan 2007

Methods	Eight-week, double-blind, randomised, multicentre study followed by a 1 week, double-blind, down-titration period
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 26 on Montgomery-Asberg Depression Rating Scale (MADRS) and a minimum score of 4 on the Clinical Global Impression-Severity. Age range: 18-80 years. Exclusion criteria: any Axis I disorder than MDD, a recent history or current diagnosis of drug or alcohol dependence, current suicidal ideation (a score of 5 or 6 on item 10 of the MADRS) or suicide attempt within the past year, history of any psychotic disorder or psychotic features, any personality disorder of sufficient severity to interfere with the participation in the study, a history of seizure disorder or any condition that predisposes to the risk of seizure, any history of narrow-angle glaucoma, a history of inappropriate antidiuretic hormone secretion syndrome, a current diagnosis or history of any clinically significant medical illness that had not been stable for at least the past year, pregnancy or breast feeding, women of childbearing potential that were not using a medically accepted form of contraception, use of a depot antipsychotic within the past 6 months, use of Benzodiazepines within 4 weeks, any antipsychotic, antidepressant or anxiolytic medication within the past 2 weeks (5 weeks for fluoxetine), participation in a previous clinical study or failure to respond to treatment with either escitalopram or duloxetine, failure to respond to adequate trials of two or more antidepressants, treatment with an investigational drug within the past month, electroconvulsive therapy within the past 3 months, initiation or termination of any type of psychotherapy within the past 3 months, concomitant use of any psychoactive drug (or any drug with a psychotropic component)
Interventions	Escitalopram: 140 participants. Duloxetine: 138 participants. Escitalopram dose range: 10-20 mg/day. Duloxetine dose: 60 mg/day. Zolpidem or zaleplon for sleep were allowed.

Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcome: Hamilton Depression Rating Scale (24 item)
Notes	This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Blinding? All outcomes	Unclear	No information provided
Incomplete outcome data addressed? All outcomes	Yes	Quote: "ITT population, which included patients who had at least one post-baseline assessment on the MADRS total score"
Free of selective reporting?	Yes	

Lepola 2003

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a total score on Montgomery-Asberg Depression Rating Scale (MADRS) between 22 and 40. Age range: 18-65 years. Exclusion criteria: mania or any bipolar disorder, schizophrenia or any psychotic disorder, obsessive-compulsive disorder, eating disorder, mental retardation, any pervasive developmental disorder or cognitive disorder (according to DSM-IV criteria), MADRS score >= 5 on item 10, treatment with antipsychotics, antidepressants, hypnotics, anxiolytics, barbiturates, chloral hydrate or other 5-hydroxytryptamine receptor agonists, electroconvulsive treatment, treatment with behaviour therapy or psychotherapy
Interventions	Escitalopram: 156 participants. Citalopram: 161 participants. Escitalopram dose range: 10-20 mg/day. Citalopram dose range: 20-40 mg/day. Benzodiazepines for insomnia were allowed.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcomes: Clinical Global Impression - Improvement, Clinical Global Impression - Severity, MADRS Individuals Items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts)
Notes	Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Unclear	No information provided
Incomplete outcome data addressed? All outcomes	Yes	Quote: "ITT population included all randomized patients who took at least one dose of double-blind study product and who had at least one valid post-baseline MADRS assessment."
Free of selective reporting?	No	

Mao 2008

Methods	Eight-week, double-blind, randomised, multicentre study
Participants	Outpatients and inpatients of six psychiatric hospitals in China, enrolled from November 2003 to July 2004. Patients were between 18 and 65 years of age, meeting criteria for major depressive disorder as defined by DSM-IV. In addition, patients were required to have both a Clinical Global Impression of Severity (CGI-S) rating more than 4 and a HAM-D-17 total score more than 18 at both the screening and baseline study visits for inclusion. Patients were excluded if they had any current primary DSM-IV Axis I diagnosis other than MDDmajor depression or any anxiety disorder as a primary diagnosis within the year preceding enrolment; any previous diagnosis of bipolar disorder, psychosis, or schizoaffective disorder; a history of substance abuse or dependence (not including nicotine dependence) within the past year; serious suicidal risk; or a serious medical illness (cardiovascular, hepatic, renal, respiratory, hematological, endocrinological, or neurological disease, or clinically significant laboratory abnormality), or if they were currently taking St. John's wort (Hypericum perforatum) or other Chinese herbal medicine for depression
Interventions	All patients had been drug-free for at least 14 days before starting treatment with escitalopram or fluoxetine. After the washout period, patients were randomly assigned in a 1:1 ratio to escitalopram (10 mg/day) plus placebo fluoxetine or fluoxetine (20 mg/day) plus placebo escitalopram (both administered once daily between 9:00 and 10:00 A.M.)
Outcomes	The primary outcome measure was change in the HAM-D-17 total score. The secondary outcome measure was change in the MADRS total score. Remission was defined as a HAM-D-17 total score less than 7, and response was defined as at least a 50% decrease from baseline. For the MADRS, remission was defined as a MADRS score equal to or less than 12, and response was defined by at least a 50% decrease from baseline
Notes	The hospitals and locations for the trials were Beijing Anding Hospital (Beijing), the Mental Health Institute of Peking University (Beijing), Beijing Chaoyang Hospital (Beijing), Guangzhou Brain Hospital (Guangzhou, Guandong Province), Huzhou Mental Health Center (Huzhou, Zhejiang Province), and Suzhou Guangji Hospital (Suzhou, Jiangsu Province). Escitalopram tablets were produced by H. Lundbeck A/S (Denmark). Fluoxetine tablets were produced by the Fourth Pharmaceutical Company (Changzhou) . Baseline symptom severity scores indicated a moderately to severely depressed patient population, with mean baseline HAM-D-17 scores of 24.7 in the escitalopram group and 24.1 in the fluoxetine group of patients (by contrast, MADRS mean baseline scores were 30.1 and 31.2,respectively)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "…patients were randomly assigned in a 1:1 ratio to…". Comment: probably not done
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	
Free of other bias?	Unclear	Quote: "…all statistical analyses were performed by Shanghai Apex medical research company"

Montgomery 2004

Methods	Eight-week, double-blind, randomised, multicentre study followed by a 1 week, single-blind, down-titration period
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 18 on Montgomery-Asberg Depression Rating Scale (MADRS).

	Age range: 18-85 years. Exclusion criteria: history of mania or any bipolar disorder, schizophrenia or any psychotic disorder, currently obsessive-compulsive disorder, eating disorders, mental retardation, any pervasive development disorder or cognitive disorder, MADRS score >= 5 on item 10, alcohol or drug abuse problems within the past 12 months, concomitant treatment with antipsychotics, antidepressants, psychotropics, serotonin receptor agonists, lithium, carbamazepine, valproate, valpromide, electroconvulsive treatment, behaviour treatment or psychotherapy, pregnancy, breast feeding, use of medications thought likely to interfere with the study
Interventions	Escitalopram: 148 participants. Venlafaxine XR: 145 participants. Escitalopram dose range: 10-20 mg/day. Venlafaxine XR dose range: 75-150 mg/day. Zolpidem or stable low doses of Benzodiazepines for insomnia were allowed
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcomes: Hamilton Depression Rating Scale (24 item and 17 item), HAMD Subscale Scores (anxiety/somatization, psychomotor retardation, sleep disturbance, cognitive disturbance and melancholia), Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Allocation concealment?	Unclear	No information provided
Blinding? All outcomes	Unclear	No information provided
Incomplete outcome data addressed? All outcomes	Yes	Quote: "ITT population included all randomized patients who took at least one dose of double-blind study product and who had at least one valid post-baseline MADRS assessment."
Free of selective reporting?	No	

Moore 2005

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 30 on Montgomery-Asberg Depression Rating Scale (MADRS). Age range: 18-65 years. Exclusion criteria: primary diagnoses for any axis I disorder other than MDD, history of mania, bipolar disorder, schizophrenia or other psychotic disorder, substance abuse or dependence within the past 12 months, use of a depot antipsychotic within the past 6 months, any antipsychotic, anxiolytic or anticonvulsant medications within the past 2 weeks
Interventions	Escitalopram: 142 participants. Citalopram: 152 participants. Escitalopram dose: 20 mg/day. Citalopram dose: 40 mg/day.
Outcomes	Primary Outcome: Change from baseline to end-of-study in Montgomery-Asberg Depression Rating Scale. Secondary Outcome: Clinical Global Impression - Severity.
Notes	Remission: a score equal or less than 12 on MADRS. This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "patients were randomly assigned". Probably done
Allocation concealment?	Unclear	No information provided.
Incomplete outcome data addressed? All outcomes	Yes	Efficacy analysis on ITT population (all patients who took at least one dose of study medication and who had at least one valid post-baseline MADRS assessment
Free of selective reporting?	No	

Nierenberg 2007

Methods	Eight-week, double-blind, randomisation, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 22 on Montgomery-Asberg Depression Rating Scale (MADRS) and a minimum score of 4 on Clinical Global Impression - Severity. Age range: 18 years and over. Exclusion criteria: pregnancy, lactation, primary Axis I disorder other than MDD, an Axis II disorder considered likely to interfere with compliance to the study protocol, substance dependence (excluding nicotine and caffeine) within the past 6 months, a significant risk of suicide, clinically significant laboratory abnormalities or co-morbid medical conditions if would likely require intervention, hospitalisation or use of an excluded medication during the course of the study, a lack of response to two or more courses of antidepressant medication in the current episode with each trial at least 4 weeks in duration and at a clinically appropriate dose, a history of non-response in association with a previous adequate trial of duloxetine, escitalopram or citalopram therapy, use of monoamine oxidase inhibitor within 14 days or of fluoxetine within the past 30 days, electroconvulsive treatment (ECT) or transcranial magnetic stimulation within the past year
Interventions	Escitalopram: 274 participants. Duloxetine: 273 participants. Escitalopram dose: 10 mg/day. Duloxetine dose : 60 mg/day. Episodic use of benzodiazepines and certain hypnotics or sedatives (e.g., chloral hydrate or zolpidem) was allowed, provided that use occurred on no more than 50% of the total days between visits. Psychotherapy was permitted but initiating, stopping or changing frequency or modality after study entry was prohibited
Outcomes	Primary Outcome: Decrease from baseline in the Hamilton Rating Scale for Depression (17-item) Maier subscale (includes HAMD17 Items 1, 2, 7, 8, 9 and 10). Secondary Outcomes: Hamilton Rating Scale for Depression (17-item) total scores, HAMD17 subscales (core, anxiety/somatization, retardation/somatization, sleep), Hamilton Rating Scale for Anxiety total score, Clinical Global Impression - Severity, Patient Global Impression of Improvement
Notes	This study was funded by duloxetine manufacturer

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Allocation concealment?	Yes	Quote: "..via the Interactive Voice Response System". Probably done
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	No	Many graphs and some unclear reporting (i.e. re. sexual functioning)

SCT-MD-02

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a minimum score of 22 on Montgomery-Asberg Depression Rating Scale and a minimum score of 2 on Item 1 of Hamilton Depression Rating Scale. Age range: 18-80 years.
Interventions	Escitalopram: 129 participants. Citalopram: 128 participants. Escitalopram dose range: 10-20 mg/day. Citalopram dose range: 20-40 mg/day.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale Secondary Outcomes: Hamilton Depression Rating Scale, HAMD Depressed Mood Item, Clinical Global Impression-Improvement, Clinical Global Impression-Severity
Notes	Only unpublished data. This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Blinding? All outcomes	Unclear	Quote: "double-blind".
Incomplete outcome data addressed? All outcomes	Yes	Quote: ITT analysis ("all patients with at least one post-baseline assessment of MADRS")

SCT-MD-09

Methods	Five-week, double-blind, randomised, forced-titration, single-centre study
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a minimum score of 18 on the Hamilton Depression Rating Scale (HAMD) with a score of at least 1 on the HAMD sleep disturbance subscale. Age range: 18-55 years.
Interventions	Escitalopram: 16 participants. Fluoxetine: 14 participants. Escitalopram dose range: 10-20 mg/day. Fluoxetine dose range: 20-40 mg/day.
Outcomes	Primary Outcome: Change from baseline to day 1 and to endpoint (mean of days 33 and 34) in the number of awakenings (Polysomnogram) Secondary Outcomes: Polysomnogram (Percent Time Awake, Sleep Efficiency, Percent REM Sleep, REM Latency, REM Epochs with Eye Movements, non-REM Epochs with Eye Movements), Sleep Diary, Pittsburgh Sleep Quality Index
Notes	Only unpublished data. This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Quote: "randomized". Probably done
Blinding? All outcomes	Unclear	Quote:"double-blind"
Incomplete outcome data addressed? All outcomes	No	
Free of other bias?	No	

SCT-MD-35

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder and having a minimum score of 22 on Montgomery-Asberg Depression Rating Scale. Age range: 18-80 years.
Interventions	Escitalopram: 138 participants. Bupropion XR: 147 participants. Escitalopram dose: 4 mg/day. Bupropion XR dose: 150 mg.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale. Secondary Outcome: Hamilton Depression Rating Scale - 24 item
Notes	Only unpublished data. This study was funded by escitalopram manufacturer

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Allocation concealment?	Unclear	No information provided.
Blinding? All outcomes	Unclear	Quote: "double-blind".
Incomplete outcome data addressed? All outcomes	Yes	Quote: ITT analysis ("all patients with at least one post-baseline assessment of MADRS")
Free of selective reporting?	Unclear	No information provided.
Free of other bias?	Unclear	No information provided.

Ventura 2007

Methods	Eight-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder with an ongoing episode and having a minimum score of 22 on Montgomery-Asberg Depression Rating Scale (MADRS). Age range: 18-80 years. Exclusion criteria: significant abnormalities from physical examination, laboratory tests and electrocardiogram (ECG), pregnancy, female patients of childbearing potential that were not using a medically accepted form of contraception, lactation, a primary Axis I disorder other than MDD, a history of any DSM-IV-definied psychotic disorder, substance abuse or dependency, risk of suicide, any personality disorder considered to be of sufficient severity to interfere with participation in the study, use of a depot neuroleptic within the past 6 months, use of any neuroleptic, antidepressant or anxiolytic medication within the past 2 weeks (5 weeks for fluoxetine), previous treatment with either escitalopram or sertraline, previous failure to respond to adequate trials of any two SSRIs, previous participation in an investigational study within the past month or previous treatment with an investigational drug within the past month (or five half-lives of the drug, whichever was longer), concomitant use of any psychotropic drug (or any drug with a psychotropic component)
Interventions	Escitalopram: 107 participants. Sertraline: 108 participants. Escitalopram dose: 10 mg/day. Sertraline dose range: 50-200 mg/day. Zolpidem or zaleplon for sleep were allowed.
Outcomes	Primary Outcome: Change from baseline to week 8 in Montgomery-Asberg Depression Rating Scale.

	Secondary Outcomes: Hamilton Depression Scale- 24 item, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "randomized". Probably done
Incomplete outcome data addressed? All outcomes	Yes	ITT population (at least one dose of study medication and at least one post-baseline MADRS assessment) using the LOCF approach
Free of selective reporting?	Yes	

Wade 2007

Methods	24-week, double-blind, randomised, multicentre study.
Participants	Outpatients meeting DSM-IV criteria for Major Depressive Disorder, having a minimum score of 26 on Montgomery-Asberg Depression Rating Scale (MADRS) and a minimum score of 4 on Clinical Global Impression-Scale. Age range: 18-65 years. Exclusion criteria: bipolar disorder, psychotic disorder or features, current eating disorders, mental retardation, any pervasive developmental disorder or cognitive disorder, or alcohol or drug abuse-related disorders within the past 12 months, obsessive-compulsive disorder, post-traumatic stress disorder, panic disorder, serious suicide risk (a minimum score of 5 on item 10 of the MADRS) concomitant behaviour therapy or systematic psychotherapy, pregnancy or breastfeeding, a history of lactose intolerance, a history of hypersensitivity or non-response to citalopram or escitalopram or duloxetine or with increased intra-ocular pressure, risk of acute narrow-angle glaucoma, use within the past 2 weeks of MAOI or RIMA, SSRIs (fluoxetine within 5 weeks), SNRIs, tricyclic antidepressants, tryptophan, psychoactive herbal remedies, any drug used for augmentation of antidepressant action or any other antidepressant drugs, oral antipsychotics and anti-manic drugs, dopamine antagonists, anxiolytics, any anticonvulsant drug, serotoninergic agonists, narcotic analgesics, cardiac glycosides, type 1c anti-arrhythmics, oral anticoagulants, cimetidine, potent inhibitors of CYP2C19, CYP1A2, or medicinal products with a narrow therapeutic index predominantly metabolised by CYP2D6, use of ECT within the past 6 months
Interventions	Escitalopram: 144 participants. Duloxetine: 151 participants. Escitalopram dose: 10 mg/day. Duloxetine dose: 60 mg/day. Zolpidem, zolpiclone or zaleplon used episodically for insomnia were allowed
Outcomes	Primary Outcome: Change from baseline to week 24 in Montgomery-Asberg Depression Rating Scale (MADRS). Secondary Outcomes: Hamilton Depression Scale - 17 item, Hamilton Anxiety Scale, Clinical Global Impression - Improvement, Clinical Global Impression - Severity
Notes	This study was funded by escitalopram manufacturer.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "..computer-generated randomization list"
Allocation concealment?	Yes	Quote: "..sealed opaque envelopes …"
Blinding? All outcomes	Yes	Quote:, "all personnel and participants were blinded to treatment assignment.."

Incomplete outcome data addressed? All outcomes	Yes	ITT analysis comprising all patients who took at least one dose of study medication and had at least one valid post-baseline MADRS assessment
Free of selective reporting?	No	Some missing standard deviations

Yevtushenko 2007

Methods	6-week, prospective, randomised, double-blind, active-controlled trial was conducted at 8 psychiatric outpatient clinics across the Federation of Russia
Participants	Outpatients, aged 25 (this minimum age limit was a requirement of one of the ethics committees) to 45 years, with a diagnosis of major depressive disorder, as defined in the DSM-IV and a total score more than or equal to 25 on MADRS. Patients were not eligible if they met DSM-IV criteria for mania or any bipolar disorder, schizophrenia, or any psychotic disorder, or displayed any psychotic features, obsessive-compulsive disorder, mental retardation or any pervasive developmental disorder, eating disorder (anorexia nervosa or bulimia nervosa), dementia, or alcohol or drug abuse within the previous12 months, a history of severe drug allergy or hypersensitivity, other serious illness or sequela of serious illness, citalopram or escitalopram treatment within 60 days prior to inclusion. Patients were also excluded if they had received an oral antipsychotic drug or monoamine oxidase inhibitor within 2 weeks prior to inclusion; a depot antipsychotic preparation within 6 months prior to inclusion; an SSRI (except fluoxetine), a serotonin-noradrenaline reuptake inhibitor, or a TCA within 1 week prior to inclusion; or fluoxetine within 5 weeks before inclusion; an antiparkinsonian compound, barbiturate, chloral hydrate, lithium, anticonvulsant, or hypnotic and anxiolytic (except for benzodiazepines used for insomnia at a stable dose for the previous 6 months or used episodically at a lower recommended dose). Women who were pregnant or breast feeding were also excluded from the study
Interventions	Using equal (~110 patients per group) block randomization, patients were assigned to receive a once-daily fixed dose of escitalopram 10 mg (109 participants), citalopram10 mg (111 participants), or citalopram 20 mg (110 participants) for 6 weeks
Outcomes	The primary efficacy measure was the change in the MADRS total score from baseline to end of study. Secondary efficacy measures were changes from baseline in MADRS total score in a subgroup of severely depressed patients (MADRS total score more than or equal to 35), MADRS core depression subscale score (in the overall population and severely depressed subgroup), CGI-S, andCGI-I. In addition, the proportions of patients classified a priori as responders (decrease in MADRS total score by at least 50% of the baseline value) or remitters (primary definition, MADRS total score less than or equal to 12; secondary definition, less than or equal to 10) were analysed
Notes	The present study was part of the S-citalopram development program for approval in some European countries through a bridging procedure using results from studies of the racemate, citalopram. Care and medication were free of charge for the patients enrolled in the trial. This study was specifically designed a priori as a superiority study. The sample size was calculated using Singer's method. The largest between-group difference was estimated at 5 points, with an SD of 12. Given this assumption, and with an a level of 5% (2-tailed) and a b level of 20%, it was calculated that 100 patients per arm would be needed to achieve sufficient power. Assuming a 10% withdrawal rate, 10 additional patients per arm were included in the design to ensure sufficient power, giving 110 patients per arm (330 patients in total). This research was sponsored by OOO ARBACOM (Moscow, Federation of Russia) (it's unclear the relationship with the escitalopram manufacturer)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "…Eight block randomizations were generated, 1 per center." Probably done
Blinding? All outcomes	Yes	Quote: "To maintain blinding, all study medication was provided in capsules

			(tablets were encapsulated in a lactose powder) that were identical in appearance, taste, and odor.Investigators and patients were blinded to treatment."
Incomplete outcome data addressed? All outcomes	Yes		LOCF method of replacing missing values
Free of selective reporting?	Yes		

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 Escitalopram versus other SSRIs	13		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	6	1823	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.89]
1.2 Versus Fluoxetine	3	783	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.60, 1.10]
1.3 Versus Paroxetine	2	784	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.61, 1.32]
1.4 Versus Sertraline	2	489	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.53]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	842	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.69, 1.20]
2.2 Versus Duloxetine	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.20]
2.3 Versus Venlafaxine XR	2	495	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.53, 1.39]

Comparison 2
Failure to respond (at 1-4 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	1	240	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.52, 2.56]
1.1 Versus Fluoxetine	1	240	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.52, 2.56]
2 Escitalopram versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Venlafaxine XR	1	293	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.47, 1.55]

Comparison 3
Failure to respond (at 16-24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	357	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.60, 1.56]
1.2 Versus Paroxetine	1	459	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.47, 1.15]
2 Escitalopram versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Duloxetine	1	295	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.42, 1.25]

Comparison 4
Failure to remission at endpoint (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	13		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	6	1823	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.36, 0.90]
1.2 Versus Fluoxetine	3	783	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.65, 1.15]
1.3 Versus Paroxetine	2	784	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.45, 1.68]
1.4 Versus Sertraline	2	489	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.81, 1.67]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	842	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.67, 1.32]
2.2 Versus Duloxetine	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.62, 1.29]
2.3 Versus Venlafaxine XR	2	495	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.63, 1.33]

Comparison 5
Failure to remission (at 16-24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Duloxetine	1	295	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.45, 1.16]

Comparison 6
Standardised mean difference at endpoint (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only’
1.1 Versus Citalopram	5	1392	Std. Mean Difference (IV, Random, 95% CI)	−0.17 [−0.30, −0.04]
1.2 Versus Fluoxetine	3	759	Std. Mean Difference (IV, Random, 95% CI)	−0.17 [−0.32, −0.03]
1.3 Versus Paroxetine	2	772	Std. Mean Difference (IV, Random, 95% CI)	−0.05 [−0.36, 0.26]
1.4 Versus Setraline	2	477	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.16, 0.20]
2 Escitalopram versus newer ADs	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	793	Std. Mean Difference (IV, Random, 95% CI)	−0.08 [−0.22, 0.05]
2.2 Versus Duloxetine	3	1096	Std. Mean Difference (IV, Random, 95% CI)	−0.10 [−0.30, 0.09]
2.3 Versus Venlafaxine XR	2	483	Std. Mean Difference (IV, Random, 95% CI)	−0.07 [−0.38, 0.25]

Comparison 7
Failure to complete (any cause)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram vs. other SSRIs	14		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	6	1823	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.56, 1.10]
1.2 Versus Fluoxetine	4	813	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.51, 1.55]
1.3 Versus Paroxetine	2	784	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.36, 1.29]
1.4 Versus Sertraline	2	489	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.78, 1.97]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	842	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.75, 1.39]
2.2 Versus Duloxetine	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.38, 0.99]
2.3 Versus Venlafaxine XR	2	495	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.39]

Comparison 8
Failure to complete (due to inefficacy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	12		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	5	1604	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.27, 2.03]
1.2 Versus Fluoxetine	4	812	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.15, 2.15]
1.3 Versus Paroxetine	2	784	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.17, 11.44]
1.4 Versus Sertraline	1	274	Odds Ratio (M-H, Random, 95% CI)	3.09 [0.32, 30.08]
2 Escitalopram versus newer ADs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	1	276	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.01, 2.02]
2.2 Versus Duloxetine	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.21, 4.25]
2.3 Versus Venlafaxine XR	1	293	Odds Ratio (M-H, Random, 95% CI)	9.06 [0.48, 169.85]

Comparison 9
Failure to complete (due to side effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram vs. other SSRIs	13		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	5	1604	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.47, 1.31]
1.2 Versus Fluoxetine	4	813	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.44, 1.28]
1.3 Versus Paroxetine	2	784	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.25, 1.96]
1.4 Versus Sertraline	2	489	Odds Ratio (M-H, Random, 95% CI)	1.08 [0.35, 3.37]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	842	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.25, 1.65]
2.2 Versus Duloxetine	3	1020	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.18, 1.29]
2.3 Versus Venlafaxine XR	2	495	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.14, 1.17]

Comparison 10
SE - Subjects with at least one TEAE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	13		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	6	1802	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.58, 1.07]
1.2 Versus Fluoxetine	4	804	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.59, 1.07]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.52, 1.17]
1.4 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.33, 1.19]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	822	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.07]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.67, 1.38]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.28, 1.23]

Comparison 11
SE - Agitation / anxiety

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	4.38 [0.48, 39.64]
1.2 Versus Fluoxetine	2	534	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.26, 1.47]
2 Escitalopram versus newer ADs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	557	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.06, 5.32]
2.2 Versus Duloxetine	2	817	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.15, 1.19]
2.3 Versus Venlafaxine XR	1	289	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.24, 2.14]

Comparison 12
SE - Constipation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	2	663	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.29, 2.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Versus Fluoxetine	2	534	Odds Ratio (M-H, Random, 95% CI)	0.50 [0.19, 1.28]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.14, 1.14]
2 Escitalopram versus newer ADs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	557	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.69]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.34, 1.40]
2.3 Versus Venlafaxine XR	1	289	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.05, 1.12]

Comparison 13
SE - ire

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	4	1226	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.55, 1.30]
1.2 Versus Fluoxetine	3	564	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.30, 1.93]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.31, 1.21]
1.4 Versus Setraline	2	483	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.84]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	822	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.86, 2.45]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.75, 1.63]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.35, 2.59]

Comparison 14
SE - Dry mouth

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	12		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	5	1442	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.61, 1.58]
1.2 Versus Fluoxetine	4	804	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.47, 1.83]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.35, 1.36]
1.4 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.15, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	822	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.39, 0.87]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.39, 0.79]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.34, 1.26]

Comparison 15
SE - Hypotension

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	3.23 [0.13, 80.02]

Comparison 16
SE - ns

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	4	1226	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.77, 1.86]
1.2 Versus Fluoxetine	2	534	Odds Ratio (M-H, Random, 95% CI)	0.79 [0.43, 1.45]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.46, 1.84]
1.4 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.59, 1.93]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	822	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.33, 0.92]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.33, 1.02]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.60]

Comparison 17
SE - Nausea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	13		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Versus Citalopram	6	1799	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.72, 1.48]
1.2 Versus Fluoxetine	4	804	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.70, 2.03]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.63, 1.46]
1.4 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.67, 1.70]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	822	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.78, 1.75]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.42, 0.75]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.14, 0.99]

Comparison 18
SE - Sleepiness/drowsiness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	10		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	5	1442	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.88, 2.72]
1.2 Versus Fluoxetine	3	774	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.62, 2.63]
1.3 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.54, 3.21]
2 Escitalopram versus newer ADs	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	557	Odds Ratio (M-H, Random, 95% CI)	1.57 [0.39, 6.39]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	1.62 [0.89, 2.94]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.22, 4.47]

Comparison 19
SE - itin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	2	609	Odds Ratio (M-H, Random, 95% CI)	1.74 [0.41, 7.48]
2 Escitalopram versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Duloxetine	2	841	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.18, 1.21]

Comparison 20
SE - Dizziness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	3	911	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.58, 3.49]
1.2 Versus Fluoxetine	3	774	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.46, 1.67]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.54, 1.97]
2 Escitalopram versus newer ADs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	557	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.33, 2.12]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.90]
2.3 Versus Venlafaxine XR	1	289	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.30, 2.41]

Comparison 21
SE - Fatigue

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	4	1148	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.62, 3.33]
1.2 Versus Fluoxetine	2	227	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.23, 2.14]
1.3 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.54, 2.25]
2 Escitalopram versus newer ADs	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	557	Odds Ratio (M-H, Random, 95% CI)	3.48 [1.77, 6.84]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.66, 1.62]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.11, 2.29]

Comparison 22
SE - Flu Syndrome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	3	932	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.40, 1.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Escitalopram versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Duloxetine	1	294	Odds Ratio (M-H, Random, 95% CI)	1.96 [0.64, 6.00]

Comparison 23
SE - Headache

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	13		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	6	1799	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.58, 1.04]
1.2 Versus Fluoxetine	4	804	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.66, 1.68]
1.3 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.81, 1.96]
1.4 Versus Sertraline	2	483	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.57, 1.48]
2 Escitalopram versus newer ADs	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	822	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.53, 1.41]
2.2 Versus Duloxetine	3	1111	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.84, 1.52]
2.3 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.73, 2.17]

Comparison 24
SE - Impotence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	2	382	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.09, 28.02]
1.2 Versus Fluoxetine	1	69	Odds Ratio (M-H, Random, 95% CI)	4.58 [0.21, 98.95]
1.3 Versus Sertraline	1	122	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.59]
2 Escitalopram versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Venlafaxine XR	2	164	Odds Ratio (M-H, Random, 95% CI)	3.67 [0.69, 19.67]

Comparison 25
SE - Jitteriness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	369	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.03, 0.82]

Comparison 26
SE - Lethargy/Sedation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	3.23 [0.13, 80.02]
1.2 Versus Sertraline	1	212	Odds Ratio (M-H, Random, 95% CI)	3.72 [0.99, 13.94]
2 Escitalopram versus newer ADs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Venlafaxine XR	1	198	Odds Ratio (M-H, Random, 95% CI)	6.46 [0.76, 54.65]

Comparison 27
SE - Decreased libido

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	248	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.32, 2.32]
1.2 Versus Fluoxetine	1	197	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.52, 6.45]
1.3 Versus Setraline	2	483	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.34, 4.15]
2 Escitalopram versus newer ADs	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Duloxetine	1	547	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.34, 1.74]
2.2 Versus Venlafaxine XR	1	198	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.23, 1.93]

Comparison 28
SE - Pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abdominal Pain	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Bupropion XR	1	278	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.23, 2.61]
1.2 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.77]
1.3 Versus Fluoxetine	1	337	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.43, 2.53]
1.4 Versus Venlafaxine XR	1	289	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.43, 4.49]
2 Back Pain	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	1	278	Odds Ratio (M-H, Random, 95% CI)	2.91 [0.58, 14.69]
2.2 Versus Citalopram	4	1289	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.38, 1.83]
2.3 Versus Duloxetine	1	270	Odds Ratio (M-H, Random, 95% CI)	2.93 [0.12, 72.67]
2.4 Versus Fluoxetine	1	337	Odds Ratio (M-H, Random, 95% CI)	1.94 [0.57, 6.57]
2.5 Versus Venlafaxine XR	1	289	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.38, 2.54]
3 Chest Pain			Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Versus Bupropion XR	1	265	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.38]
3.2 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.77]
4 Pain In Extremity	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Versus Bupropion XR	1	278	Odds Ratio (M-H, Random, 95% CI)	4.79 [0.23, 100.64]
5 Pharyngolaryngeal Pain	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 29
SE - Increased sweating

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	4	1226	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.72, 2.68]
1.2 Versus Paroxetine	1	454	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.37, 1.23]
1.3 Versus Setraline	1	271	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.26, 1.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Escitalopram versus newer ADs	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Duloxetine	2	841	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.33, 1.06]
2.2 Versus Venlafaxine XR	2	487	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.23, 0.87]

Comparison 30
SE - Yawning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	1		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	3.23 [0.13, 80.02]
2 Escitalopram versus newer ADs	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	557	Odds Ratio (M-H, Random, 95% CI)	7.71 [1.75, 34.05]
2.2 Versus Duloxetine	1	547	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.15, 1.01]

Comparison 31
Deaths, suicide and suicidality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Suicide - Tendency/ Ideation	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	1	248	Odds Ratio (M-H, Random, 95% CI)	2.98 [0.12, 73.76]
1.2 Versus Bupropion XR	1	279	Odds Ratio (M-H, Random, 95% CI)	5.18 [0.25, 108.95]
1.3 Versus Venlafaxine XR	1	198	Odds Ratio (M-H, Random, 95% CI)	3.09 [0.12, 76.83]
2 Suicide - Attempted	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Citalopram	3	974	Odds Ratio (M-H, Random, 95% CI)	1.48 [0.40, 5.45]
2.2 Versus Fluoxetine	2	437	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.10, 9.50]
2.3 Versus Venlafaxine XR	1	289	Odds Ratio (M-H, Random, 95% CI)	4.97 [0.24, 104.34]
3 Suicide - Completed	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.77]
3.2 Versus Fluoxetine	1	337	Odds Ratio (M-H, Random, 95% CI)	2.86 [0.12, 70.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 Versus Duloxetine	1	294	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.65]
4 Deaths	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Versus Citalopram	1	294	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.77]
4.2 Versus Fluoxetine	1	337	Odds Ratio (M-H, Random, 95% CI)	1.91 [0.17, 21.23]
4.3 Versus Duloxetine	2	841	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.11, 9.90]
4.4 Versus Venlafaxine XR	1	293	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.03]

Comparison 32

Sensitivity analyses - Excluding trials whose dropout rate was greater than 20%

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs (dropout rate greater than 20% in both arms)	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	4	1187	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.40, 0.79]
1.2 Versus Fluoxetine	2	578	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.13]
2 Escitalopram versus other SSRIs (dropout rate greater than 20% in only one arm)	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Citalopram	3	830	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.34, 0.72]

Comparison 33

Sensitivity analyses - Excluding trials for which the imputation methods were used - RESPONSE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	5	1566	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.46, 0.84]
1.2 Versus Fluoxetine	2	578	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.13]
1.3 Versus Paroxetine	1	325	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.70, 1.78]
1.4 Versus Sertraline	1	215	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.53]
2 Escitalopram versus newer ADs	7		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 Bupropion XR	2	566	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.45]
2.2 Versus Duloxetine	3	1120	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.20]
2.3 Versus Venlafaxine XR	2	495	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.53, 1.39]

Comparison 34
Sensitivity analyses - Excluding trials for which the imputation methods were used - REMISSION

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	4	1187	Odds Ratio (M-H, Random, 95% CI)	0.40 [0.18, 0.88]
1.2 Versus Fluoxetine	2	578	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.55, 1.25]
1.3 Versus Paroxetine	2	784	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.45, 1.68]
1.4 Versus Sertraline	1	215	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.62, 1.81]
2 Escitalopram versus newer ADs	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	2	566	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.53, 1.64]
2.2 Versus Duloxetine	2	825	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.56, 1.63]
2.3 Versus Venlafaxine XR	2	495	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.63, 1.33]

Comparison 35
Sensitivity analyses - Excluding trials for which the imputation methods were used - STANDARD DEVIATION

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Escitalopram versus other SSRIs	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Versus Citalopram	3	773	Std. Mean Difference (IV, Random, 95% CI)	−0.19 [−0.43, 0.05]
1.2 Versus Fluoxetine	2	425	Std. Mean Difference (IV, Random, 95% CI)	−0.10 [−0.29, 0.09]
1.3 Versus Paroxetine	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
1.4 Versus Setraline	2	477	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.16, 0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Escitalopram versus newer ADs	7		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Versus Bupropion XR	3	793	Std. Mean Difference (IV, Random, 95% CI)	−0.08 [−0.22, 0.05]
2.2 Versus Duloxetine	2	809	Std. Mean Difference (IV, Random, 95% CI)	−0.06 [−0.32, 0.20]
2.3 Versus Venlafaxine XR	2	483	Std. Mean Difference (IV, Random, 95% CI)	−0.07 [−0.38, 0.25]

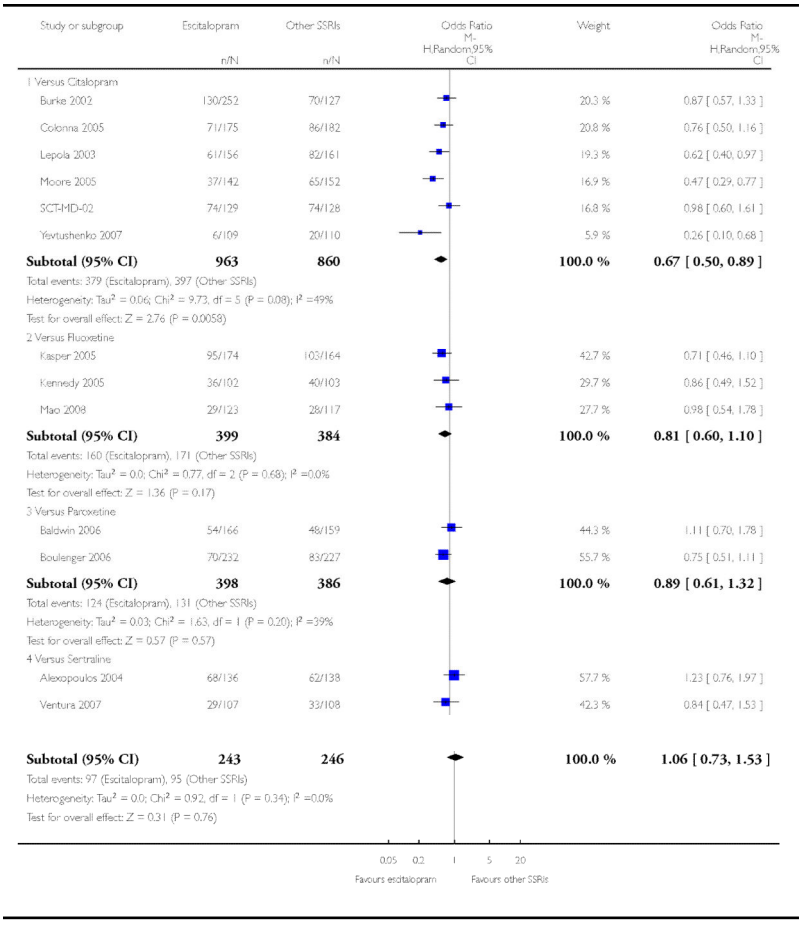
Analysis 1.1

Comparison 1 Failure to respond at endpoint (6-12 weeks), Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

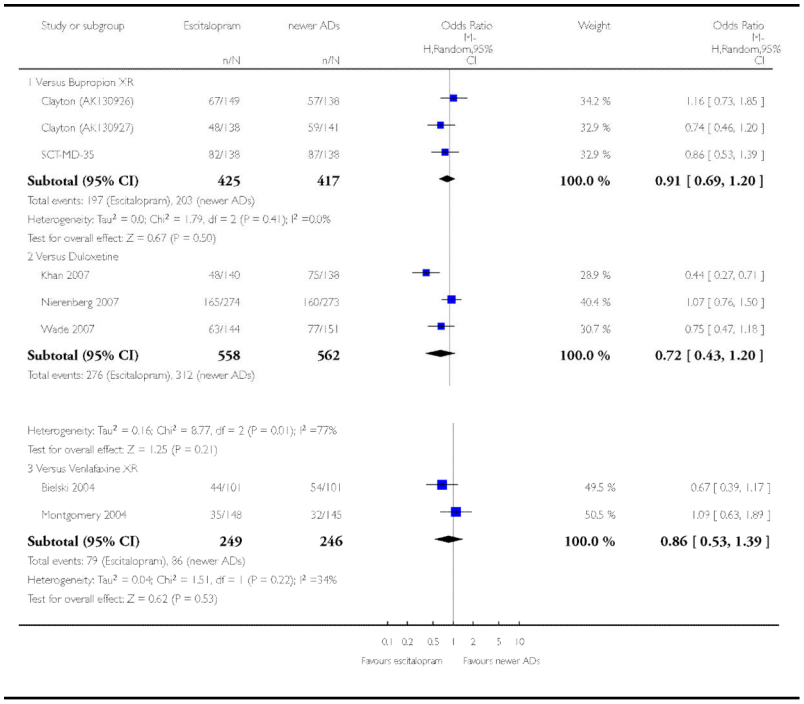
Comparison: 1 Failure to respond at endpoint (6-12 weeks)

Outcome: 1 Escitalopram versus other SSRIs



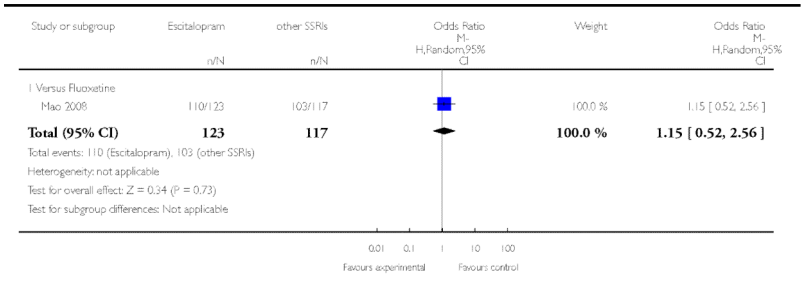
Analysis 1.2
Comparison 1 Failure to respond at endpoint (6-12 weeks), Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 1 Failure to respond at endpoint (6-12 weeks)
Outcome: 2 Escitalopram versus newer ADs



Analysis 2.1
Comparison 2 Failure to respond (at 1-4 weeks), Outcome 1 Escitalopram versus other SSRIs

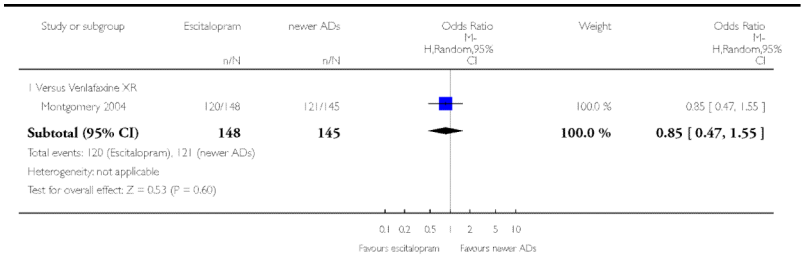
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 2 Failure to respond (at 1-4 weeks)
Outcome: 1 Escitalopram versus other SSRIs



Analysis 2.2

Comparison 2 Failure to respond (at 1-4 weeks), Outcome 2 Escitalopram versus newer ADs

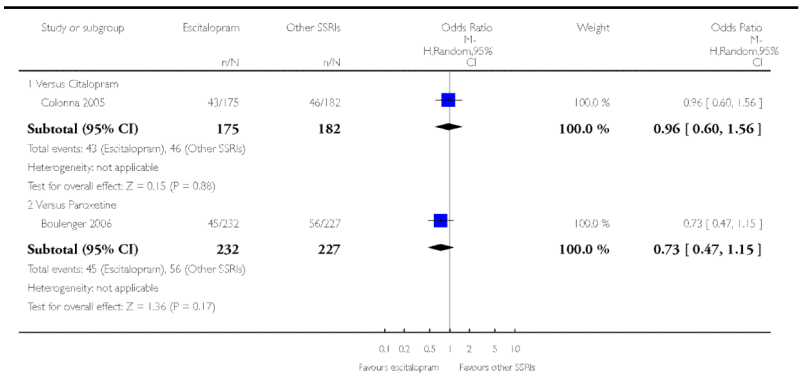
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 2 Failure to respond (at 1-4 weeks)
Outcome: 2 Escitalopram versus newer ADs



Analysis 3.1

Comparison 3 Failure to respond (at 16-24 weeks), Outcome 1 Escitalopram versus other SSRIs

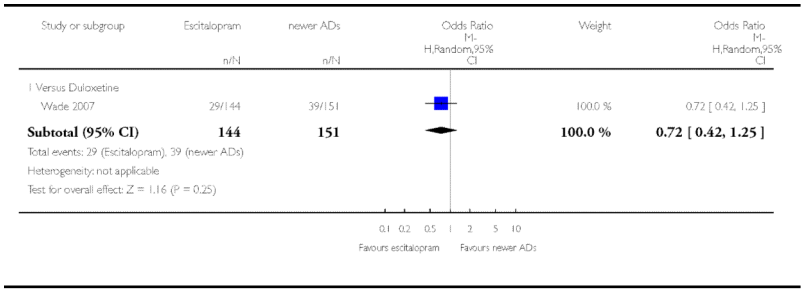
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 3 Failure to respond (at 16-24 weeks)
Outcome: 1 Escitalopram versus other SSRIs



Analysis 3.2

Comparison 3 Failure to respond (at 16-24 weeks), Outcome 2 Escitalopram versus newer ADs

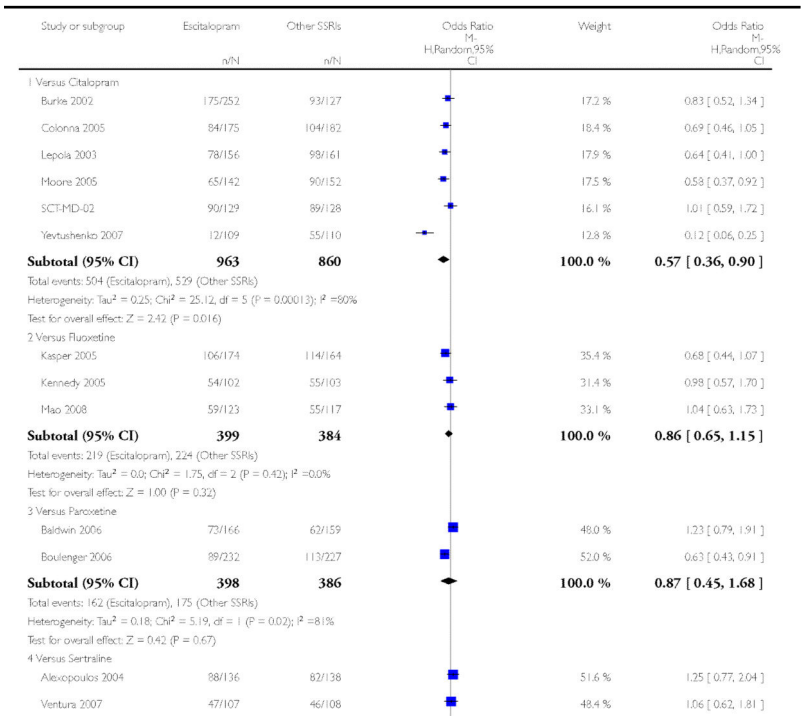
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 3 Failure to respond (at 16-24 weeks)
Outcome: 2 Escitalopram versus newer ADs

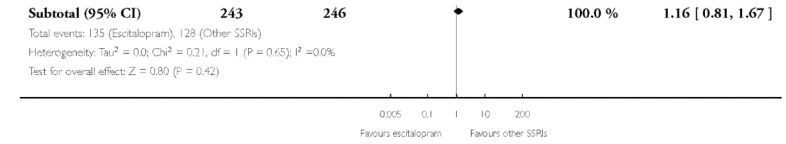


Analysis 4.1

Comparison 4 Failure to remission at endpoint (6-12 weeks), Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 4 Failure to remission at endpoint (6-12 weeks)
Outcome: 1 Escitalopram versus other SSRIs





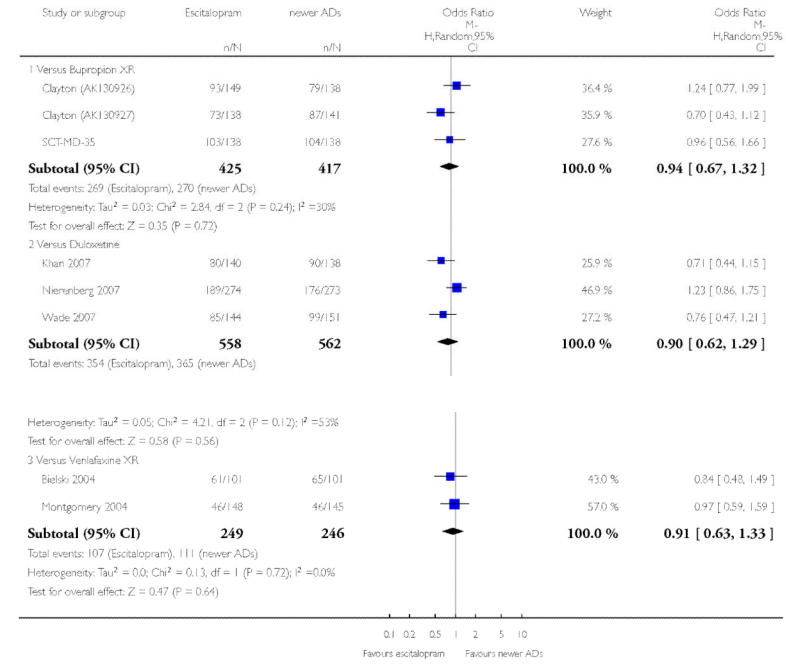
Analysis 4.2

Comparison 4 Failure to remission at endpoint (6-12 weeks), Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 4 Failure to remission at endpoint (6-12 weeks)

Outcome: 2 Escitalopram versus newer ADs



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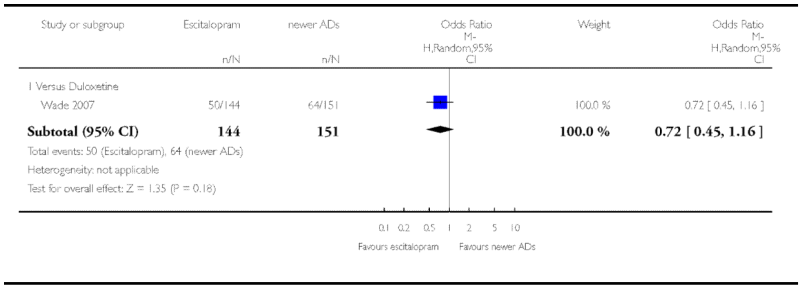
Analysis 5.1

Comparison 5 Failure to remission (at 16-24 weeks), Outcome 1 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 5 Failure to remission (at 16-24 weeks)

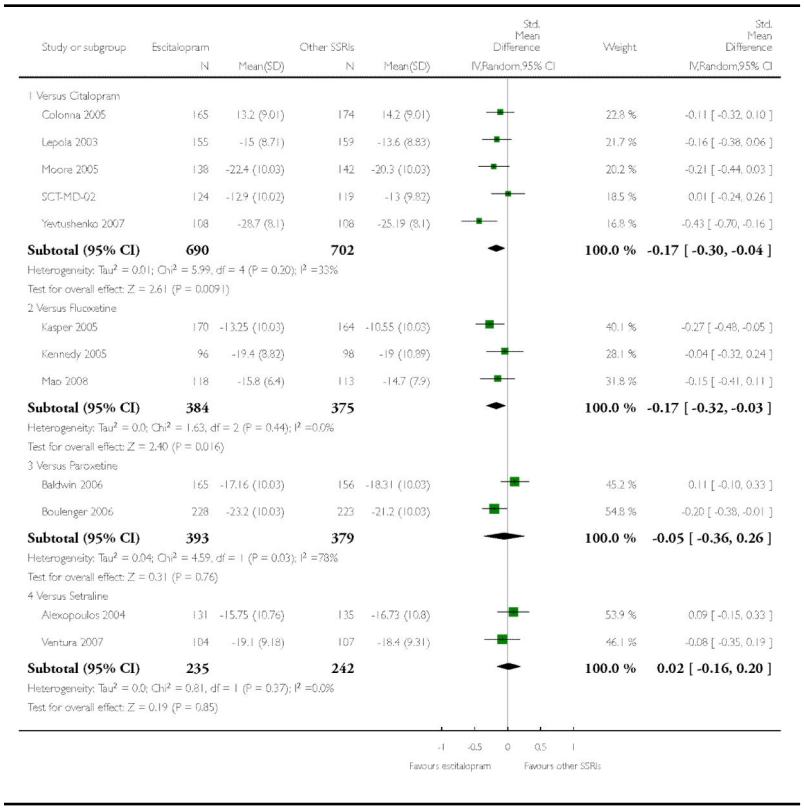
Outcome: 1 Escitalopram versus newer ADs



Analysis 6.1

Comparison 6 Standardised mean difference at endpoint (6-12 weeks), Outcome 1 Escitalopram versus other SSRIs

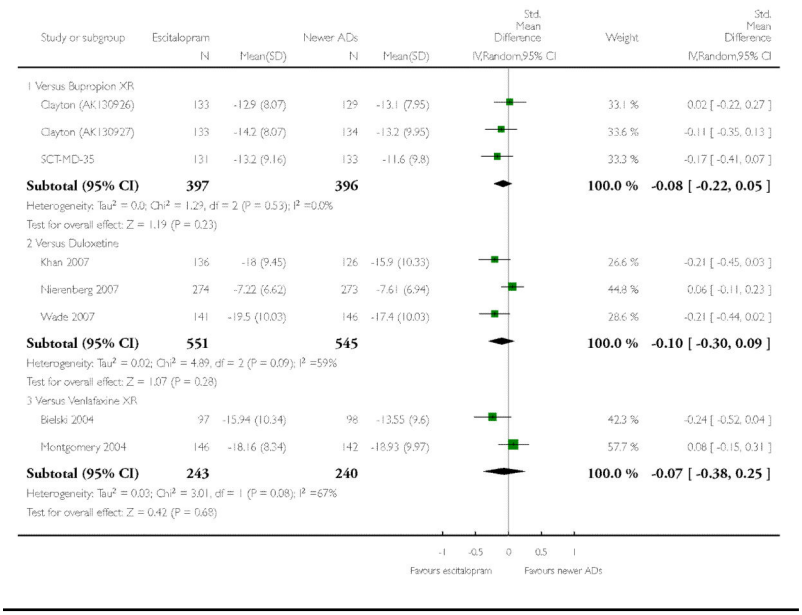
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 6 Standardised mean difference at endpoint (6-12 weeks)
Outcome: 1 Escitalopram versus other SSRIs



Analysis 6.2

Comparison 6 Standardised mean difference at endpoint (6-12 weeks), Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 6 Standardised mean difference at endpoint (6-12 weeks)
Outcome: 2 Escitalopram versus newer ADs



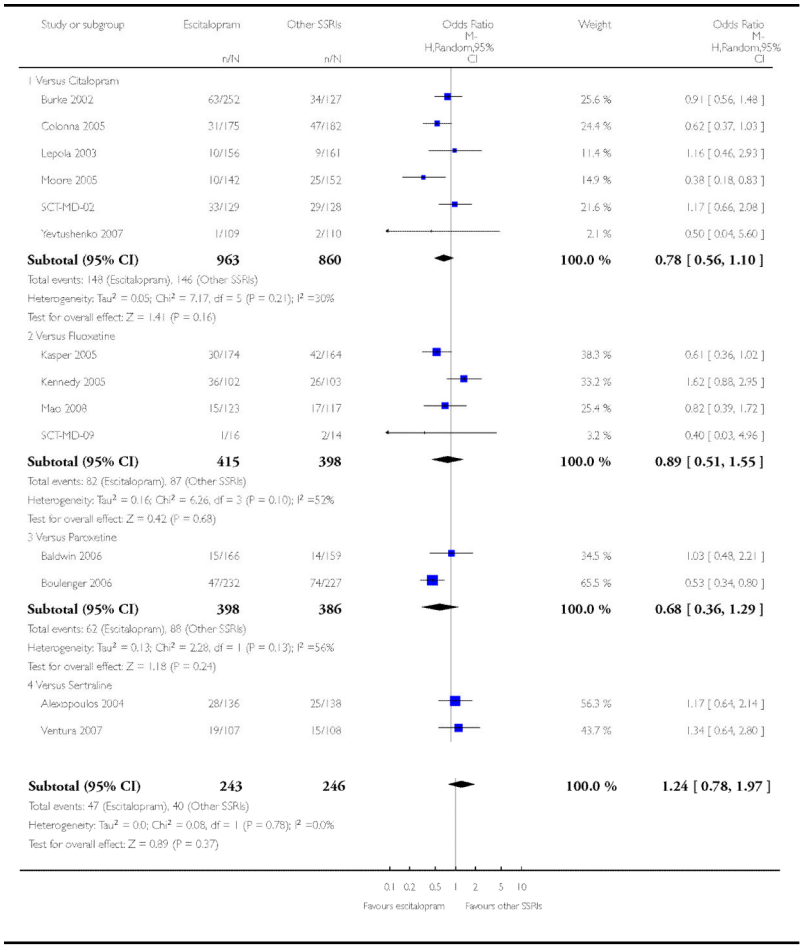
Analysis 7.1

Comparison 7 Failure to complete (any cause), Outcome 1 Escitalopram vs. other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 7 Failure to complete (any cause)

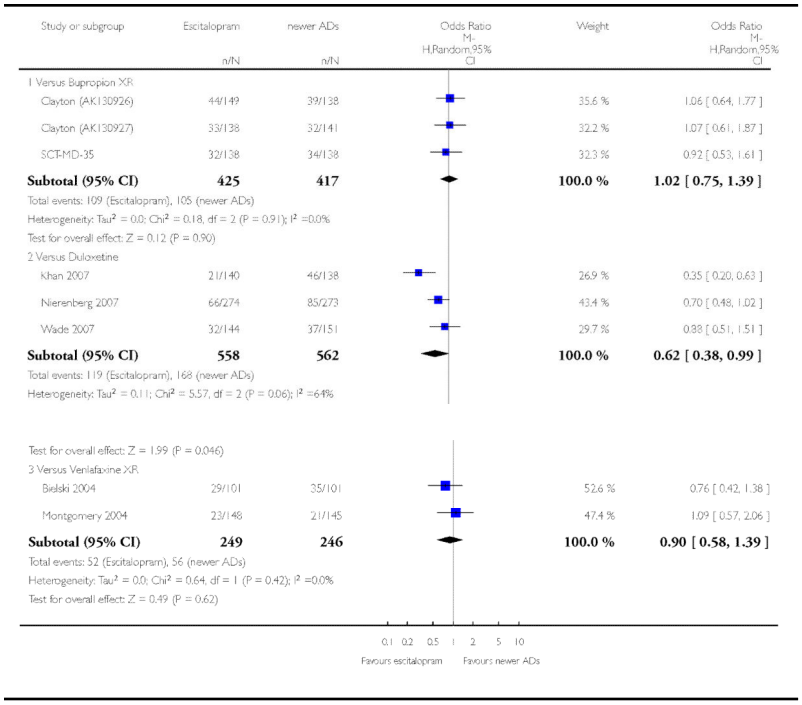
Outcome: 1 Escitalopram vs. other SSRIs



Analysis 7.2

Comparison 7 Failure to complete (any cause), Outcome 2 Escitalopram versus newer ADs

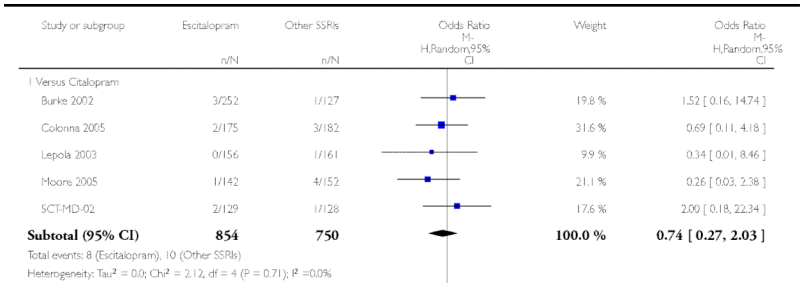
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 7 Failure to complete (any cause)
Outcome: 2 Escitalopram versus newer ADs

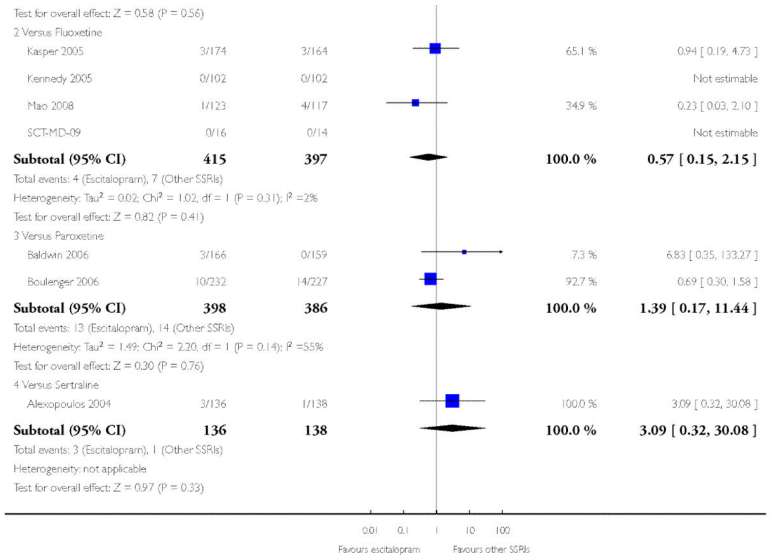


Analysis 8.1

Comparison 8 Failure to complete (due to inefficacy), Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 8 Failure to complete (due to inefficacy)
Outcome: 1 Escitalopram versus other SSRIs





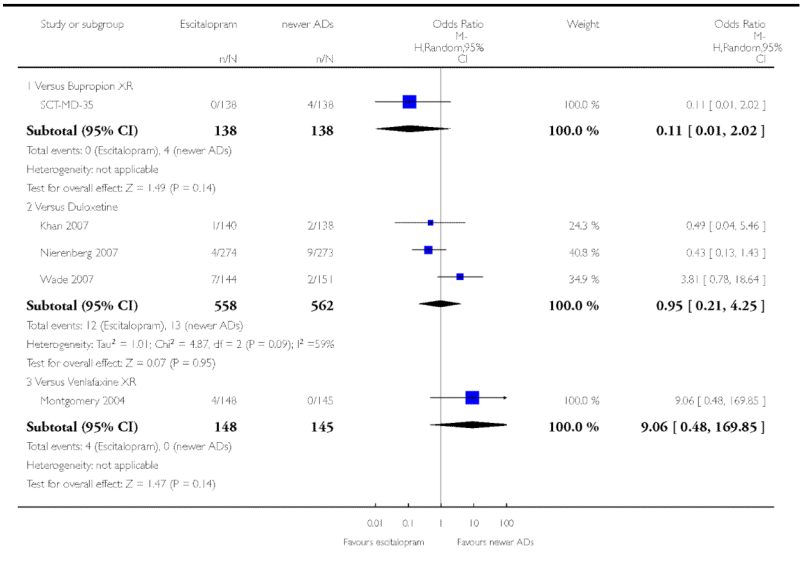
Analysis 8.2

Comparison 8 Failure to complete (due to inefficacy), Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 8 Failure to complete (due to inefficacy)

Outcome: 2 Escitalopram versus newer ADs



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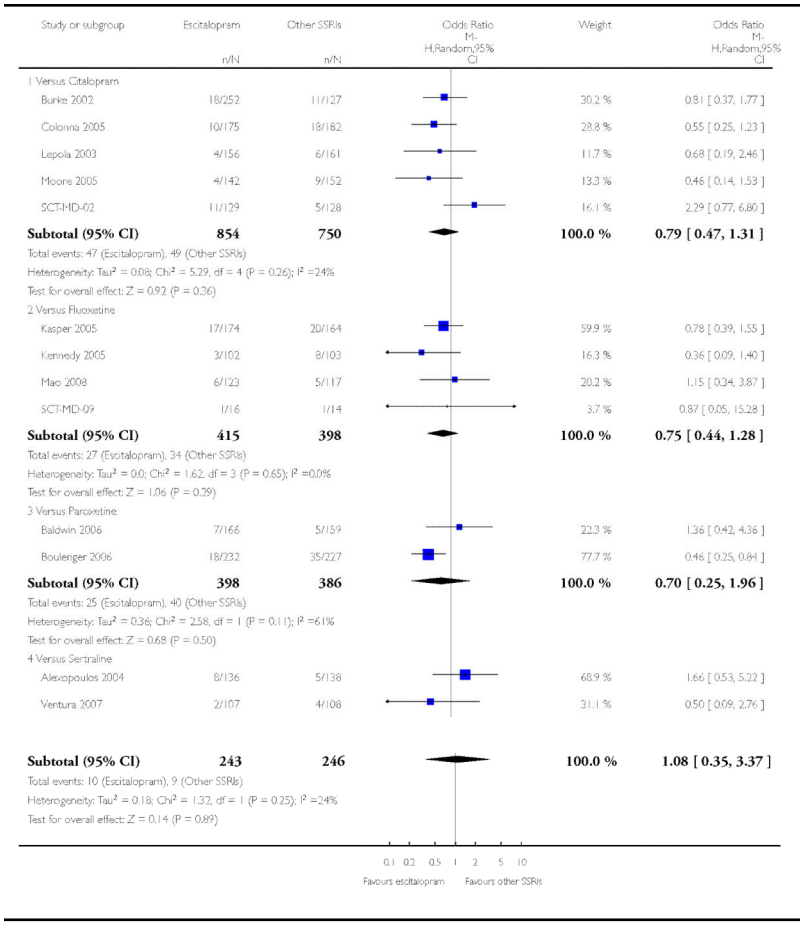
Analysis 9.1

Comparison 9 Failure to complete (due to side effects), Outcome 1 Escitalopram vs. other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 9 Failure to complete (due to side effects)

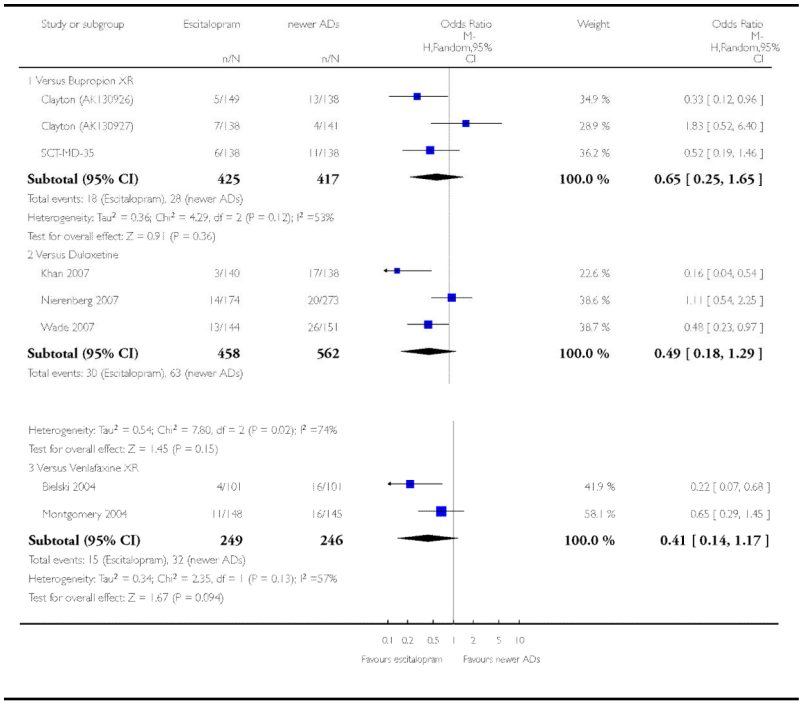
Outcome: 1 Escitalopram vs. other SSRIs



Analysis 9.2

Comparison 9 Failure to complete (due to side effects), Outcome 2 Escitalopram versus newer ADs

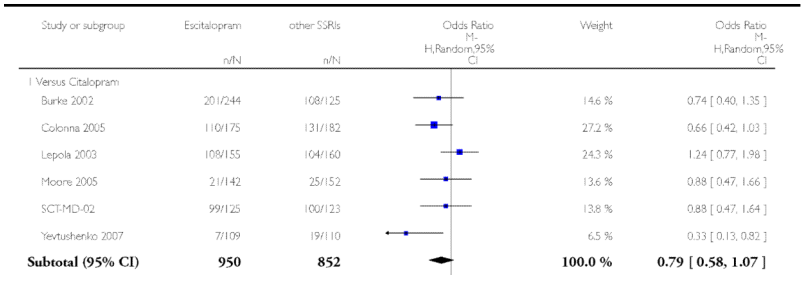
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 9 Failure to complete (due to side effects)
Outcome: 2 Escitalopram versus newer ADs

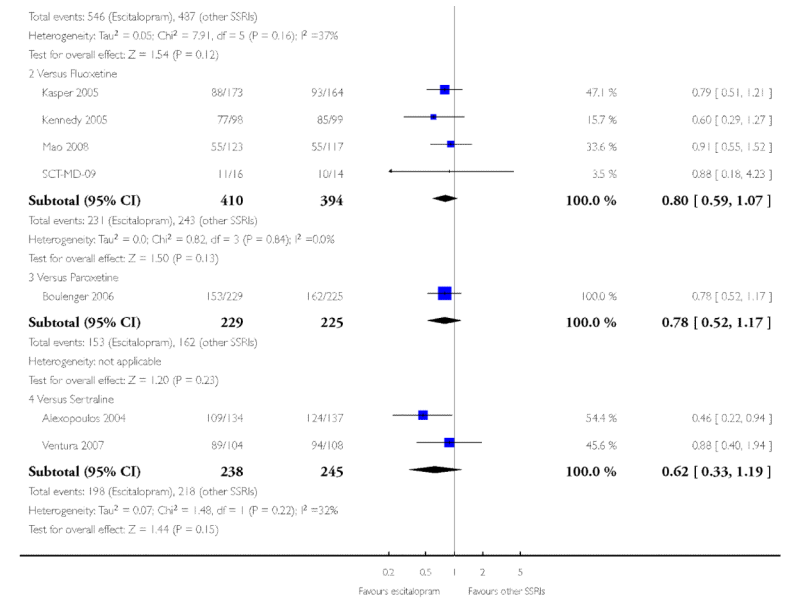


Analysis 10.1

Comparison 10 SE - Subjects with at least one TEAE, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 10 SE - Subjects with at least one TEAE
Outcome: 1 Escitalopram versus other SSRIs





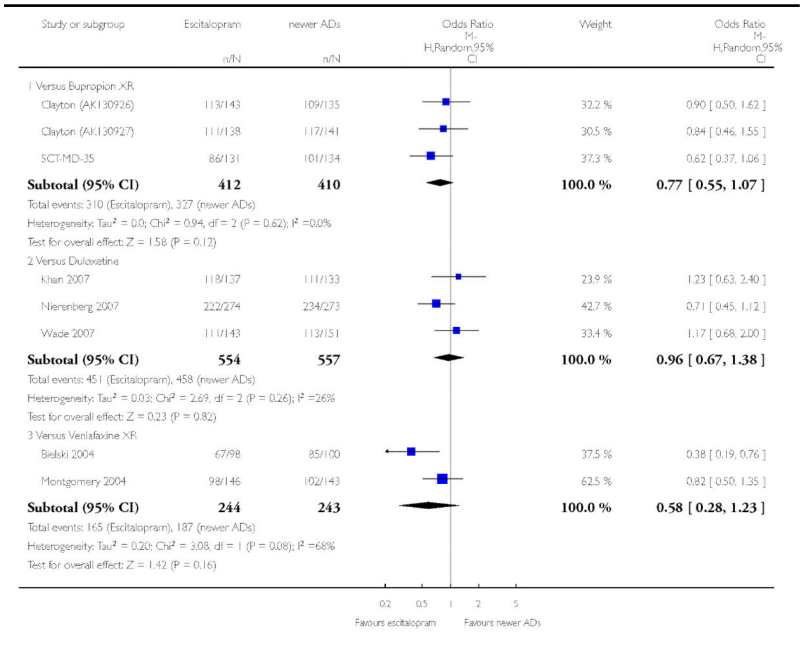
Analysis 10.2

Comparison 10 SE - Subjects with at least one TEAE, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 10 SE - Subjects with at least one TEAE

Outcome: 2 Escitalopram versus newer AD



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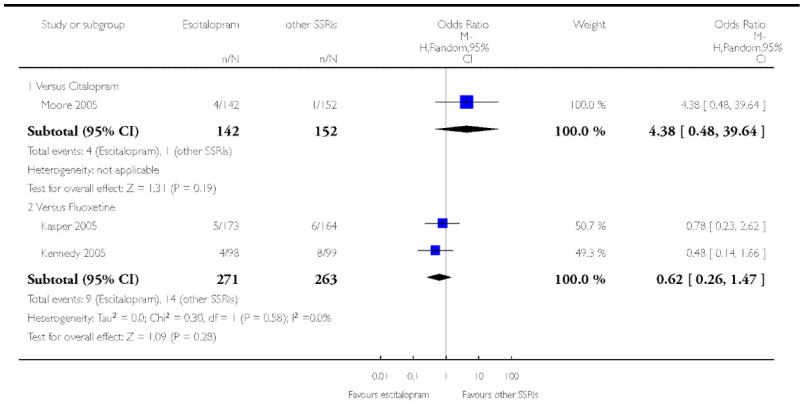
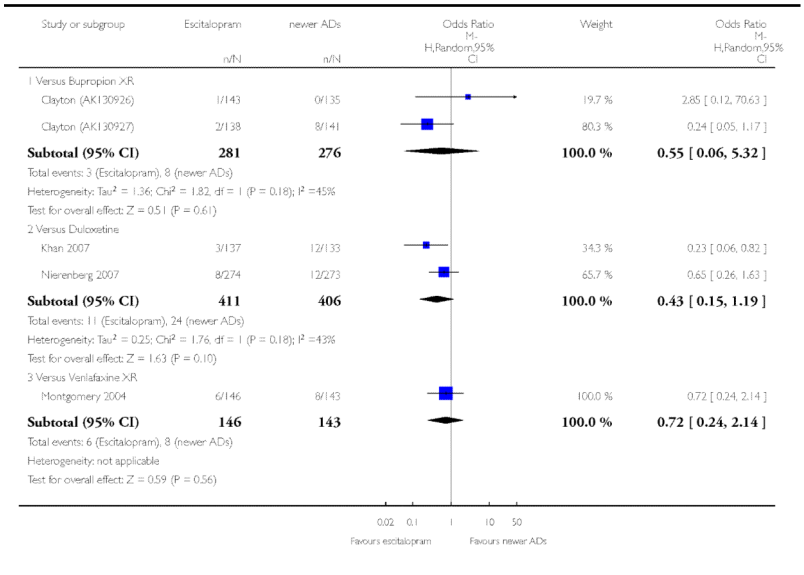
Analysis 11.1
Comparison 11 SE - Agitation / anxiety, Outcome 1
Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 11 SE - Agitation / anxiety
Outcome: 1 Escitalopram versus other SSRIs



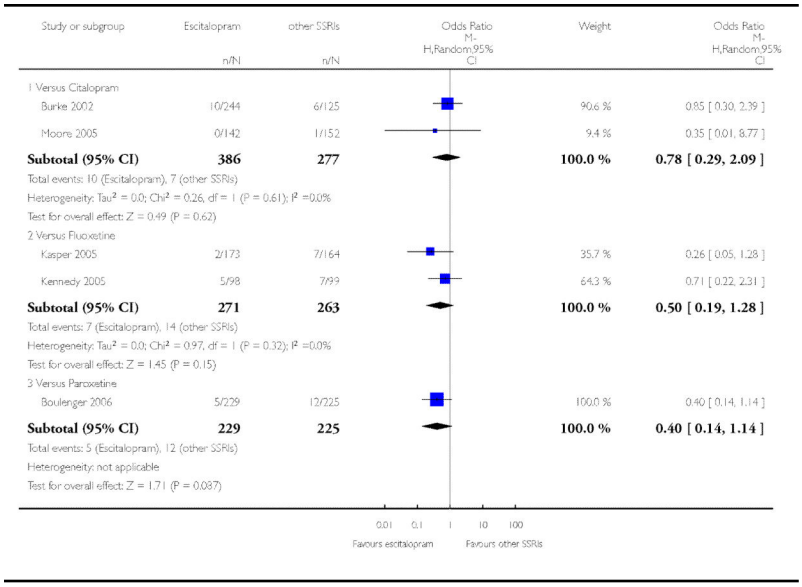
Analysis 11.2
Comparison 11 SE - Agitation / anxiety, Outcome 2
Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 11 SE - Agitation / anxiety
Outcome: 2 Escitalopram versus newer ADs



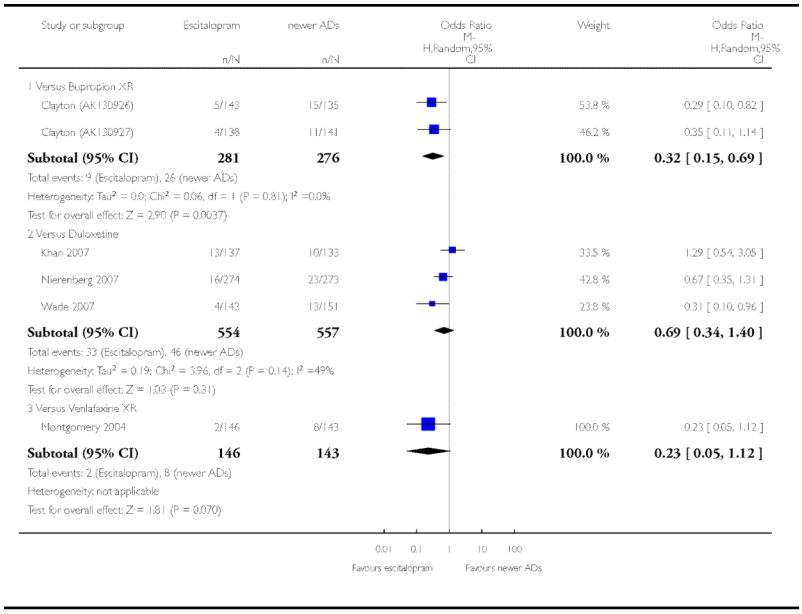
Analysis 12.1
Comparison 12 SE - Constipation, Outcome 1
Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 12 SE - Constipation
Outcome: 1 Escitalopram versus other SSRIs



Analysis 12.2
Comparison 12 SE - Constipation, Outcome 2
Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 12 SE - Constipation
Outcome: 2 Escitalopram versus newer AD



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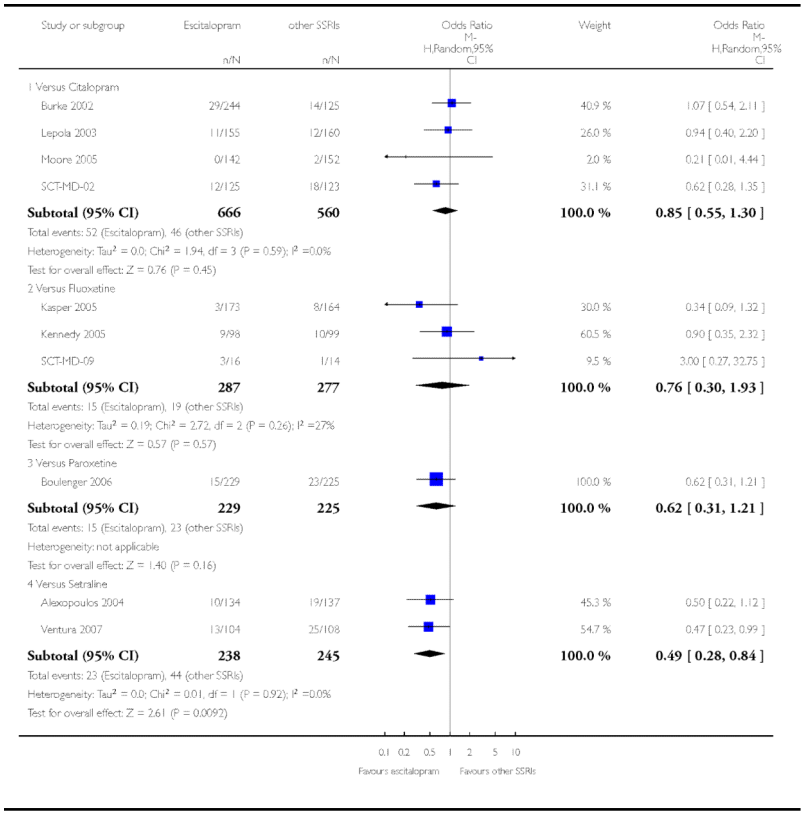
Analysis 13.1
Comparison 13 SE - Diarrhoea, Outcome 1
Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 13 SE - Diarrhoea
Outcome: 1 Escitalopram versus other SSRIs



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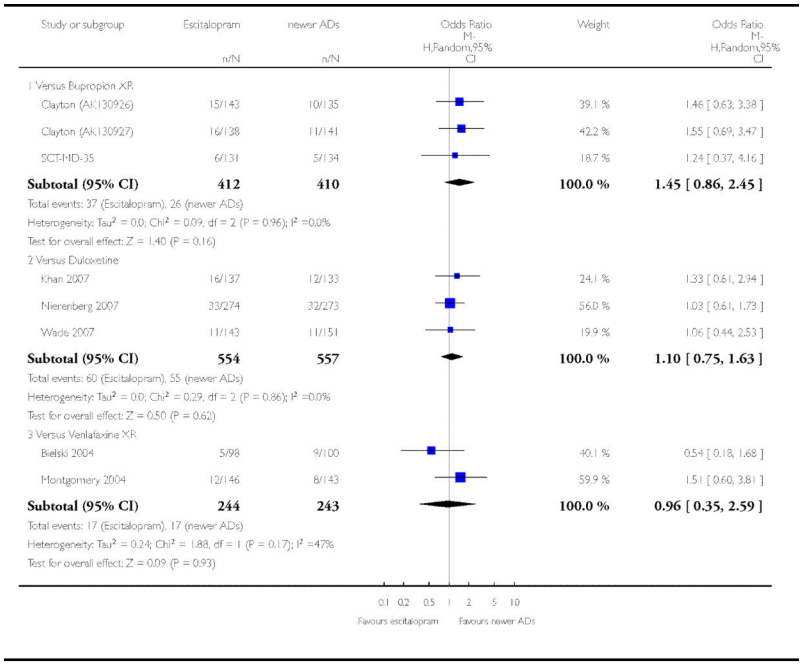
Analysis 13.2
Comparison 13 SE - Diarrhoea, Outcome 2
Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 13 SE - Diarrhoea
Outcome: 2 Escitalopram versus newer ADs

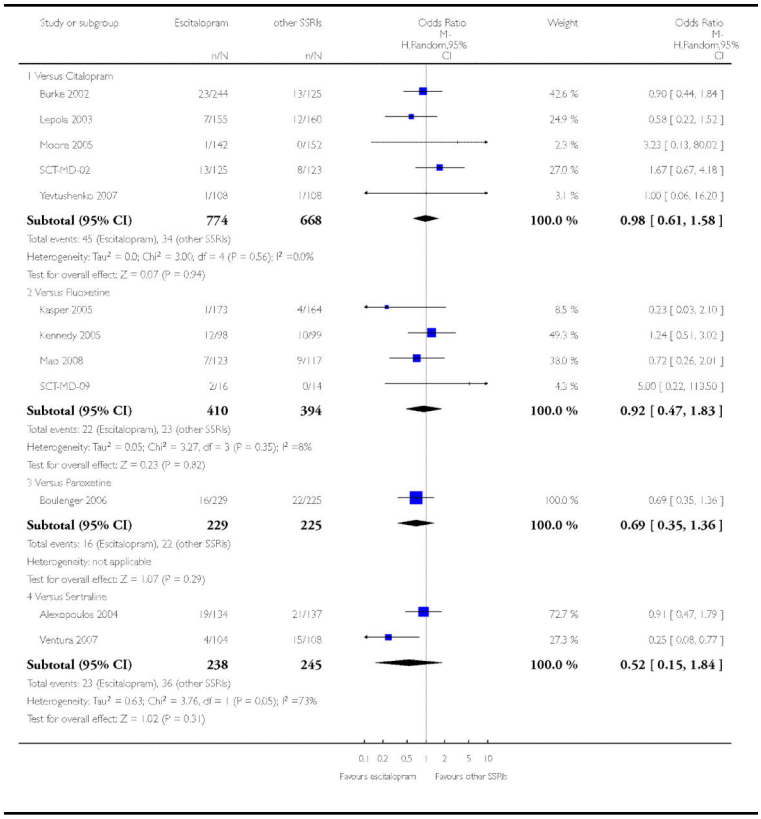


Analysis 14.1
Comparison 14 SE - Dry mouth, Outcome 1
Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 14 SE - Dry mouth

Outcome: 1 Escitalopram versus other SSRIs



Analysis 14.2

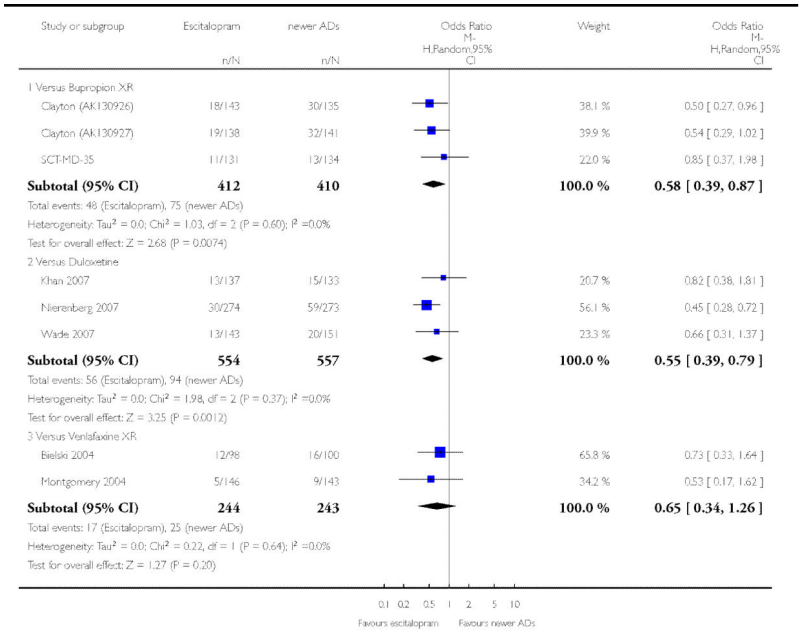
Comparison 14 SE - Dry mouth, Outcome 2

Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 14 SE - Dry mouth

Outcome: 2 Escitalopram versus newer AD



Analysis 15.1

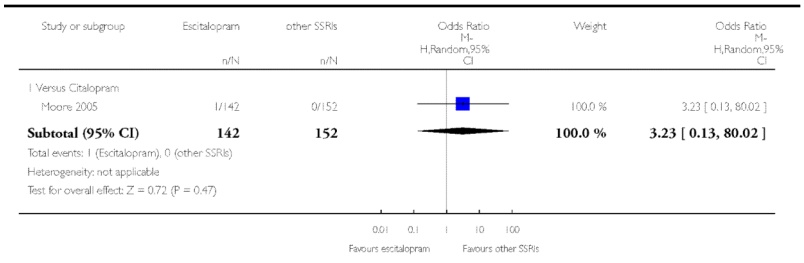
Comparison 15 SE - Hypotension, Outcome 1

Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 15 SE - Hypotension

Outcome: 1 Escitalopram versus other SSRIs



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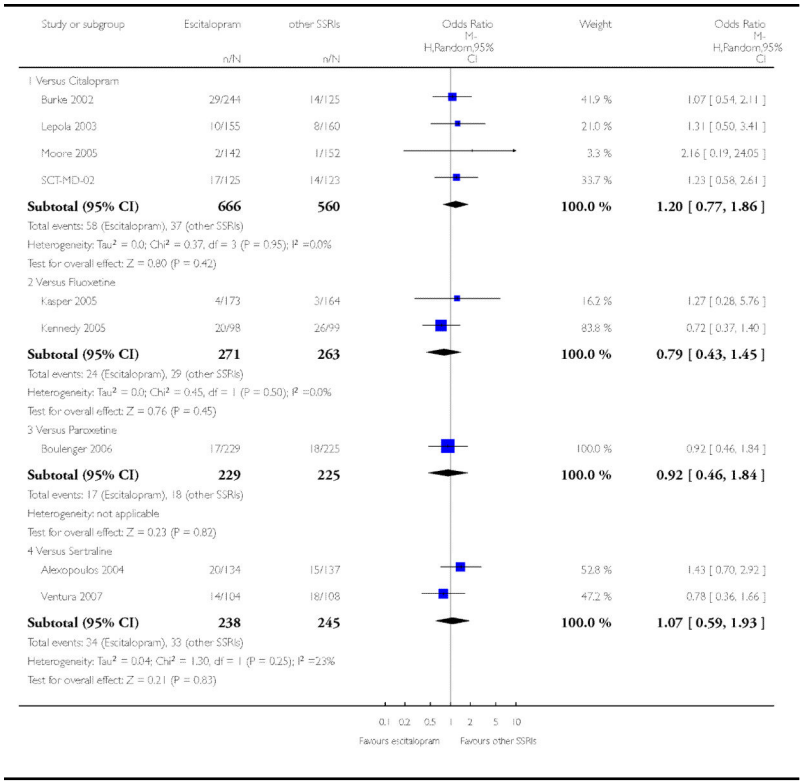
Analysis 16.1

Comparison 16 SE - Insomnia, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 16 SE - Insomnia

Outcome: 1 Escitalopram versus other SSRIs



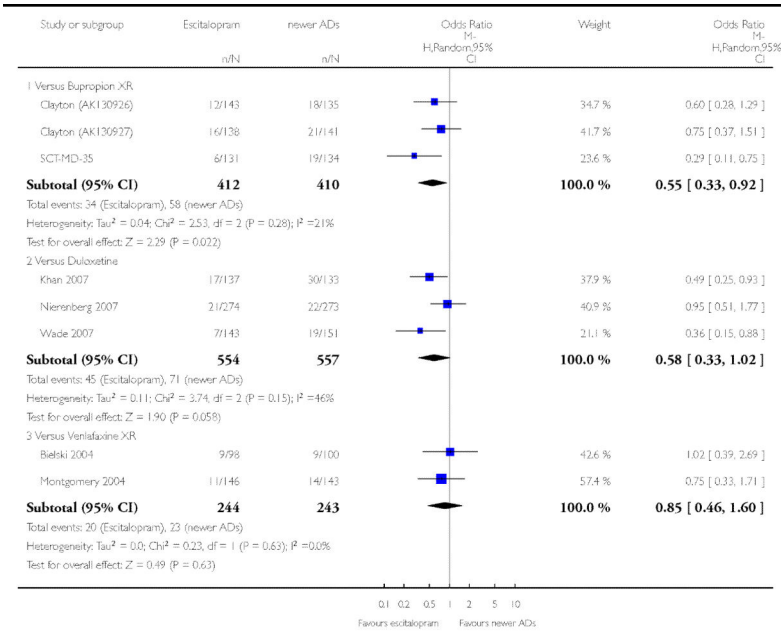
Analysis 16.2

Comparison 16 SE - Insomnia, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 16 SE - Insomnia

Outcome: 2 Escitalopram versus newer ADs



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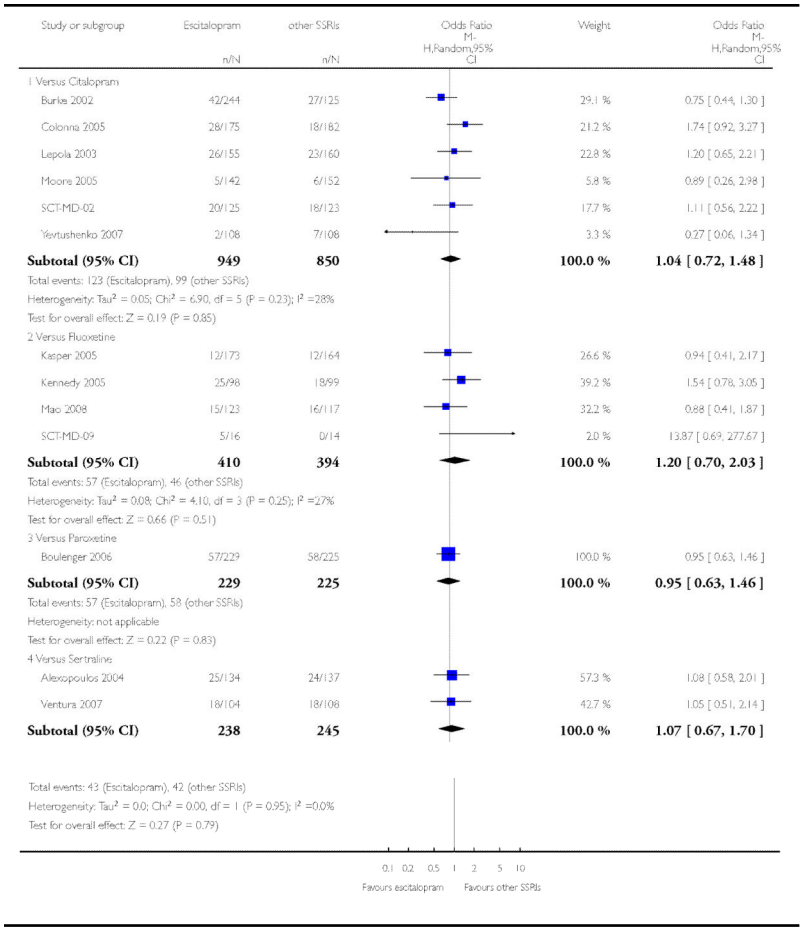
Analysis 17.1

Comparison 17 SE - Nausea, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 17 SE - Nausea

Outcome: 1 Escitalopram versus other SSRIs



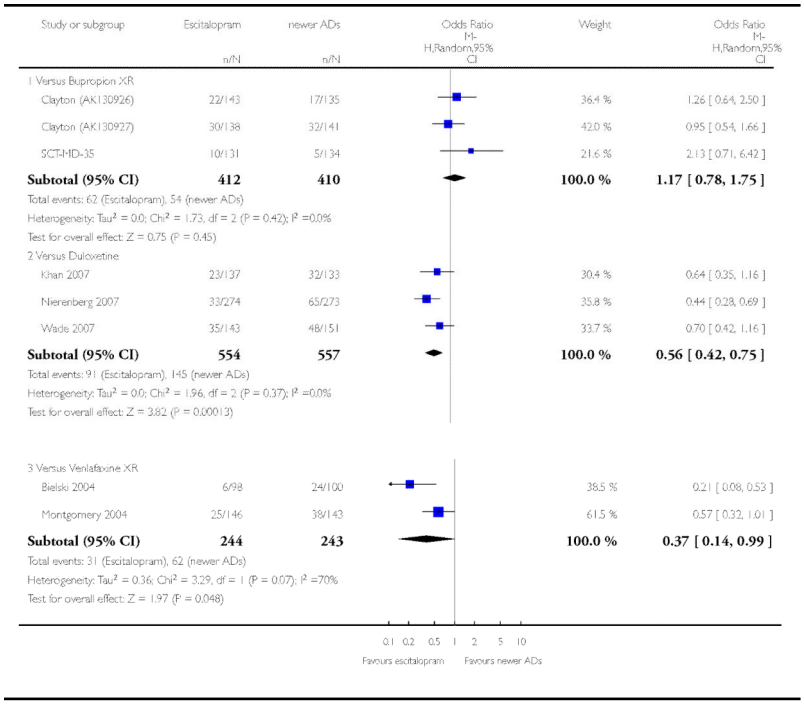
Analysis 17.2

Comparison 17 SE - Nausea, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 17 SE - Nausea

Outcome: 2 Escitalopram versus newer ADs



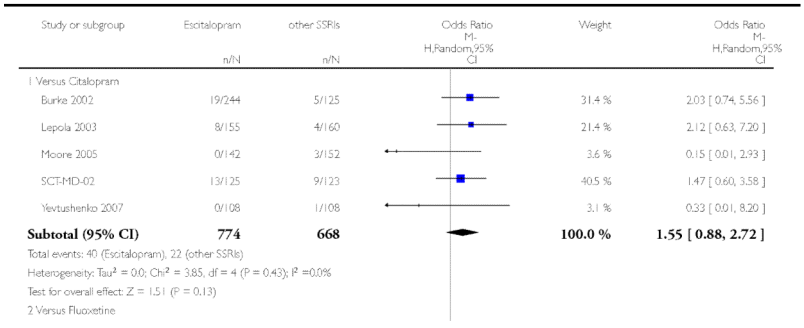
Analysis 18.1

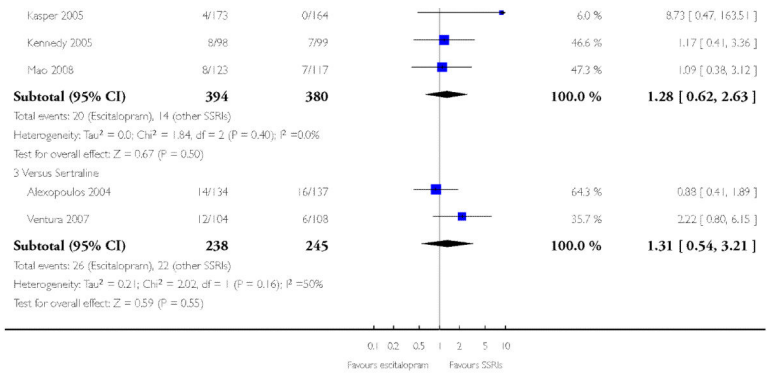
Comparison 18 SE - Sleepiness/drowsiness, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 18 SE - Sleepiness/drowsiness

Outcome: 1 Escitalopram versus other SSRIs





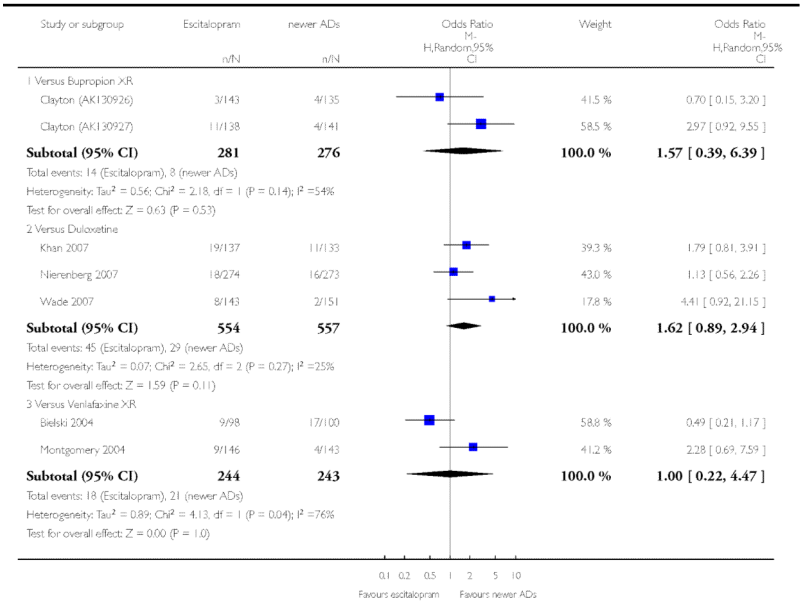
Analysis 18.2

Comparison 18 SE - Sleepiness/drowsiness, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 18 SE - Sleepiness/drowsiness

Outcome: 2 Escitalopram versus newer ADs



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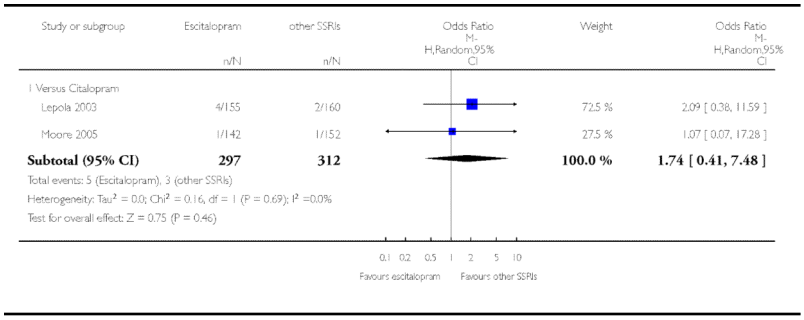
Analysis 19.1

Comparison 19 SE - Vomiting, Outcome 1 Escitalopram versus other SSRIs

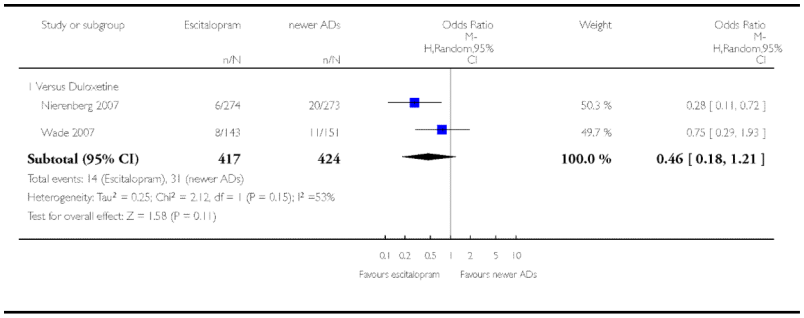
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 19 SE - Vomiting
Outcome: 1 Escitalopram versus other SSRIs



Analysis 19.2

Comparison 19 SE - Vomiting, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 19 SE - Vomiting
Outcome: 2 Escitalopram versus newer ADs



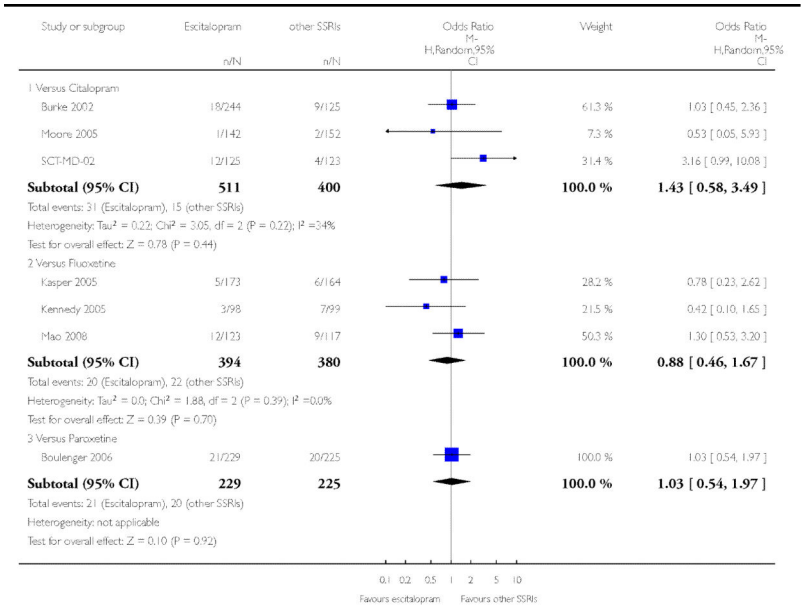
Analysis 20.1

Comparison 20 SE - Dizziness, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 20 SE - Dizziness

Outcome: 1 Escitalopram versus other SSRIs



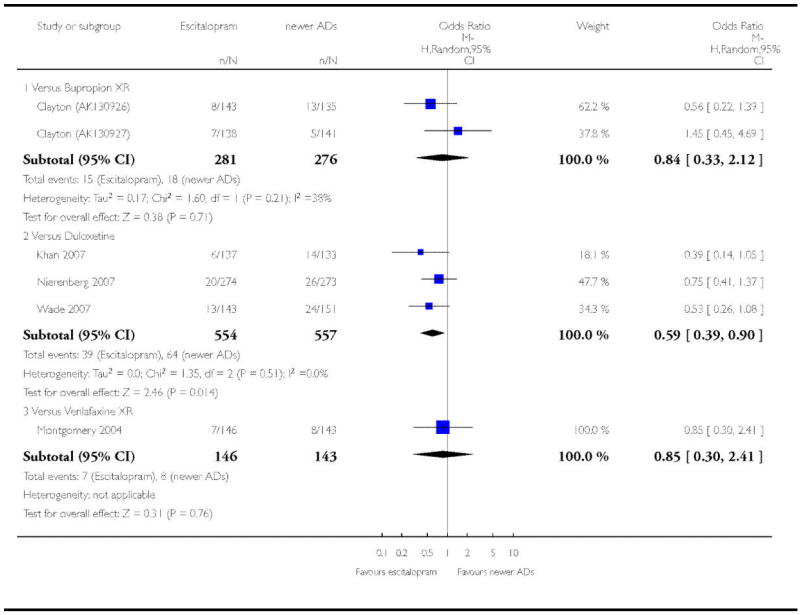
Analysis 20.2

Comparison 20 SE - Dizziness, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 20 SE - Dizziness

Outcome: 2 Escitalopram versus newer ADs



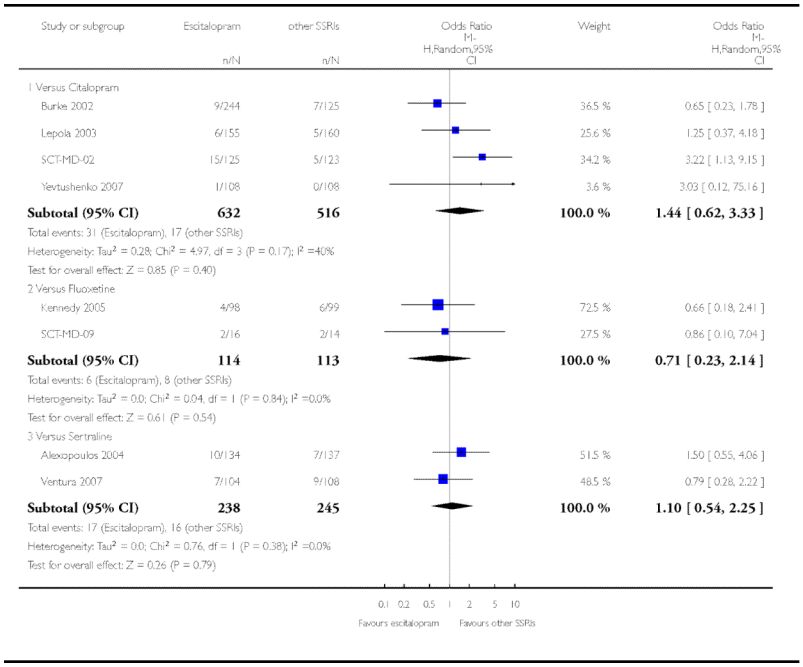
Analysis 21.1

Comparison 21 SE - Fatigue, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 21 SE - Fatigue

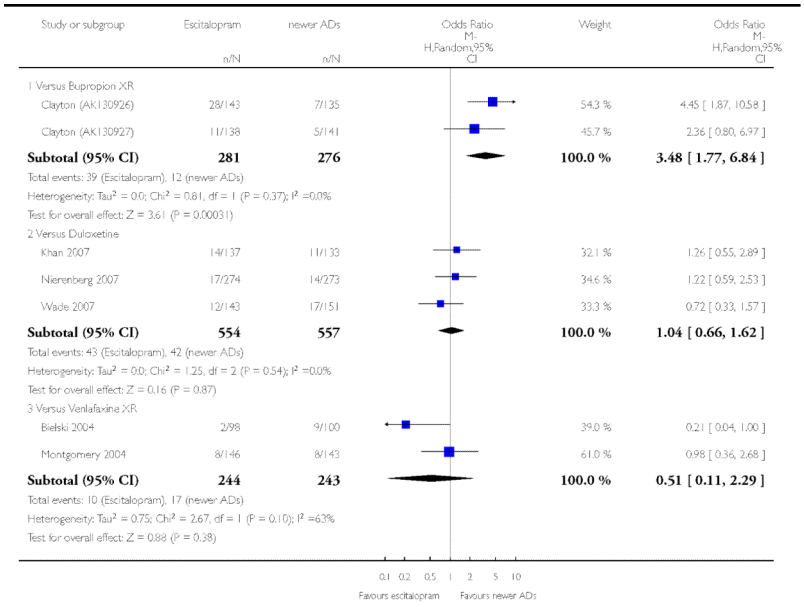
Outcome: 1 Escitalopram versus other SSRIs



Analysis 21.2

Comparison 21 SE - Fatigue, Outcome 2 Escitalopram versus newer ADs

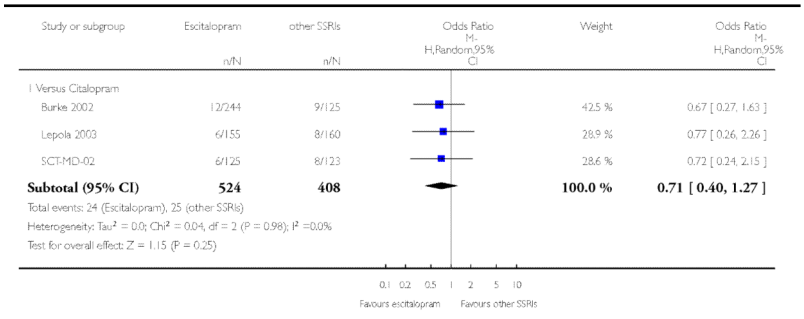
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 21 SE - Fatigue
Outcome: 2 Escitalopram versus newer ADs



Analysis 22.1

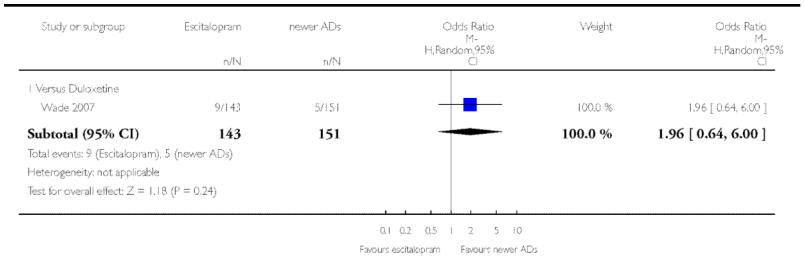
Comparison 22 SE - Flu Syndrome, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 22 SE - Flu Syndrome
Outcome: 1 Escitalopram versus other SSRIs



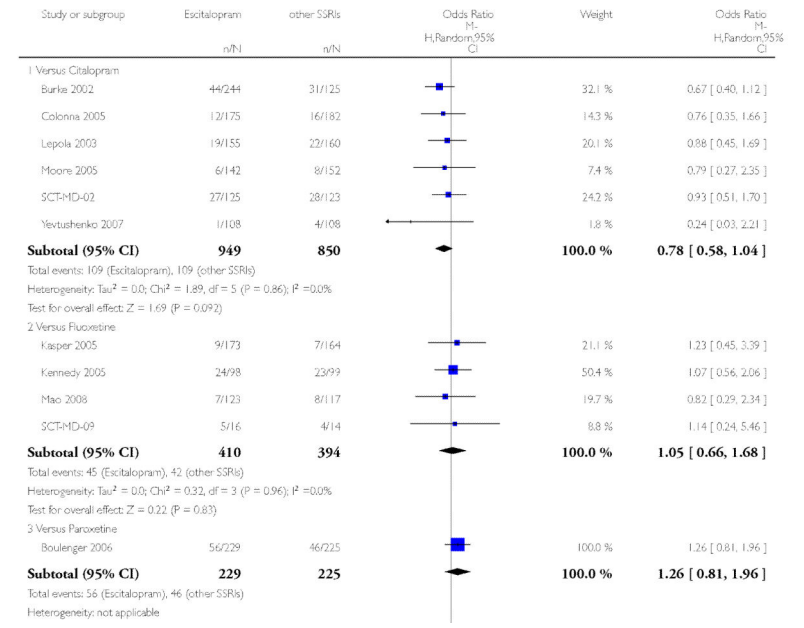
Analysis 22.2
Comparison 22 SE - Flu Syndrome, Outcome 2
Escitalopram versus newer ADs

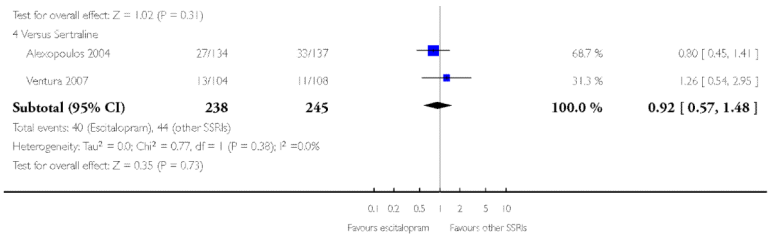
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 22 SE - Flu Syndrome
Outcome: 2 Escitalopram versus newer AD



Analysis 23.1
Comparison 23 SE - Headache, Outcome 1
Escitalopram versus other SSRIs

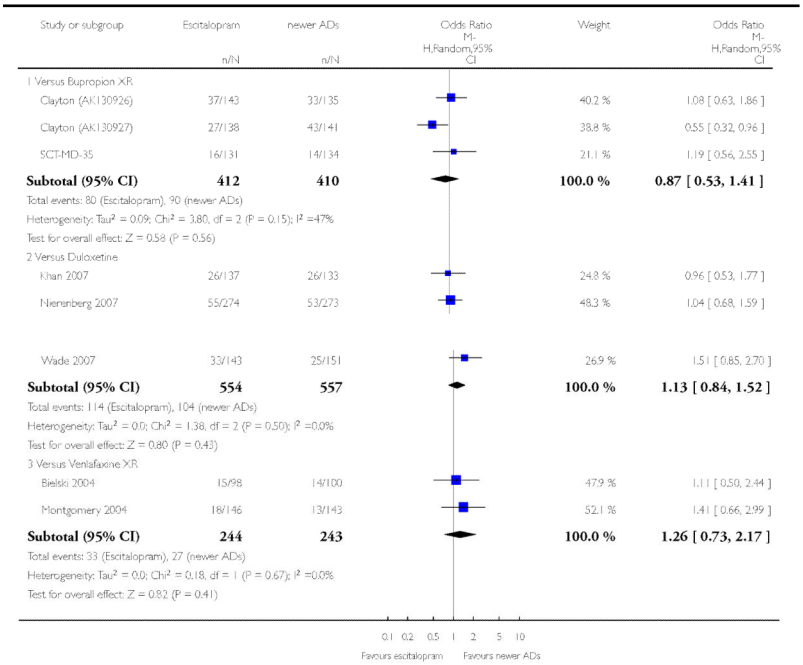
Review: Escitalopram versus other antidepressive agents for depression
Comparison: 23 SE - Headache
Outcome: 1 Escitalopram versus other SSRIs





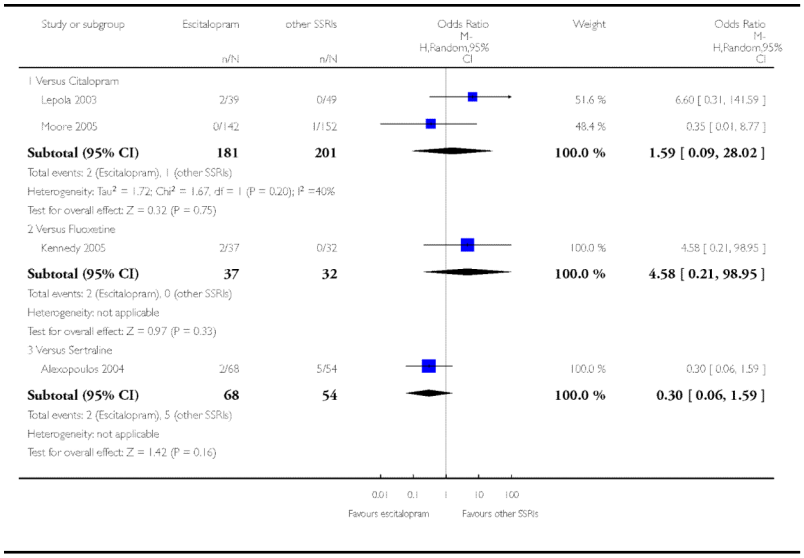
Analysis 23.2
Comparison 23 SE - Headache, Outcome 2
Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 23 SE - Headache
Outcome: 2 Escitalopram versus newer ADs



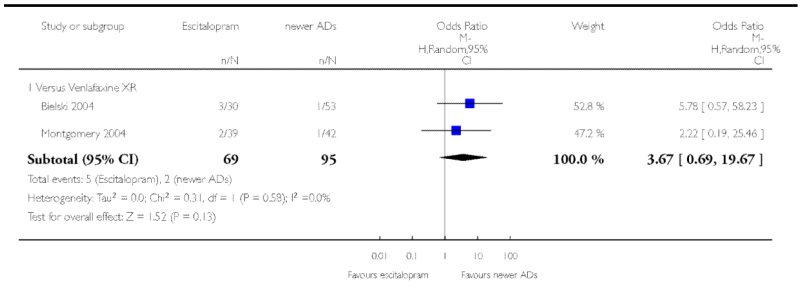
Analysis 24.1
Comparison 24 SE - Impotence, Outcome 1
Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 24 SE - Impotence
Outcome: 1 Escitalopram versus other SSRIs



Analysis 24.2
Comparison 24 SE - Impotence, Outcome 2
Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 24 SE - Impotence
Outcome: 2 Escitalopram versus newer ADs



Analysis 25.1

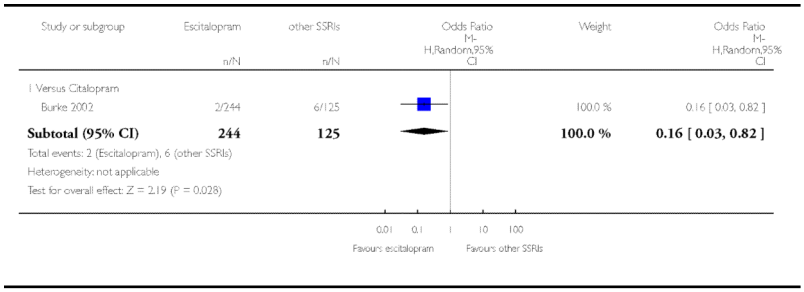
Comparison 25 SE - Jitteriness, Outcome 1

Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 25 SE - Jitteriness

Outcome: 1 Escitalopram versus other SSRIs



Analysis 26.1

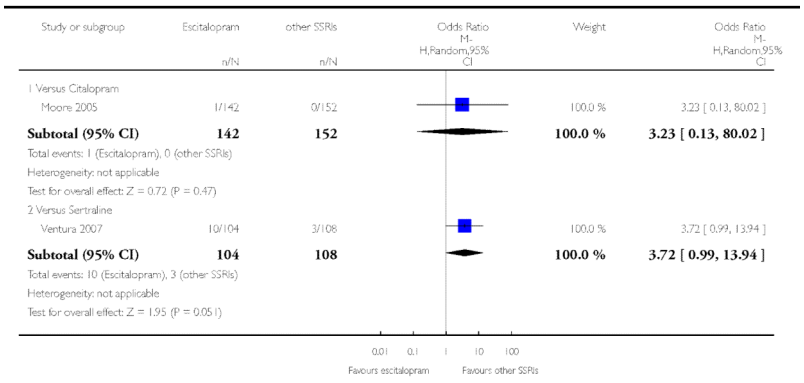
Comparison 26 SE - Lethargy/Sedation, Outcome 1

Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 26 SE - Lethargy/Sedation

Outcome: 1 Escitalopram versus other SSRIs



Analysis 26.2

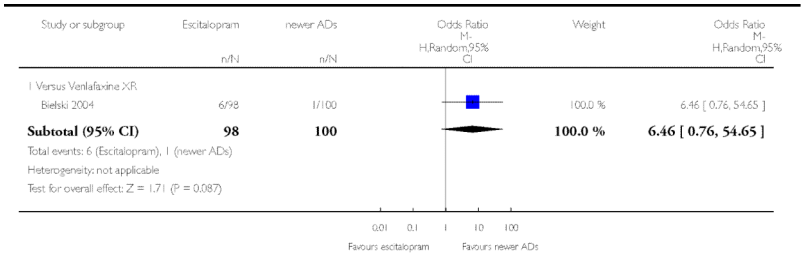
Comparison 26 SE - Lethargy/Sedation, Outcome 2

Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 26 SE - Lethargy/Sedation

Outcome: 2 Escitalopram versus newer ADs



Analysis 27.1

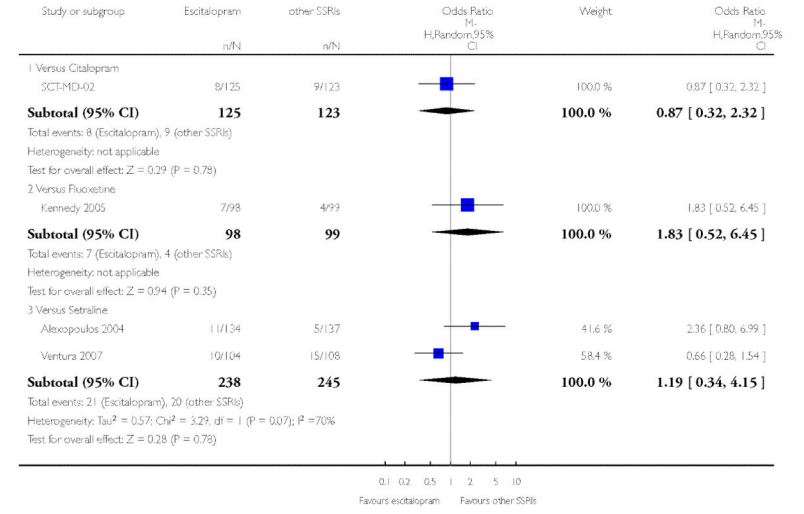
Comparison 27 SE - Decreased libido, Outcome 1

Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

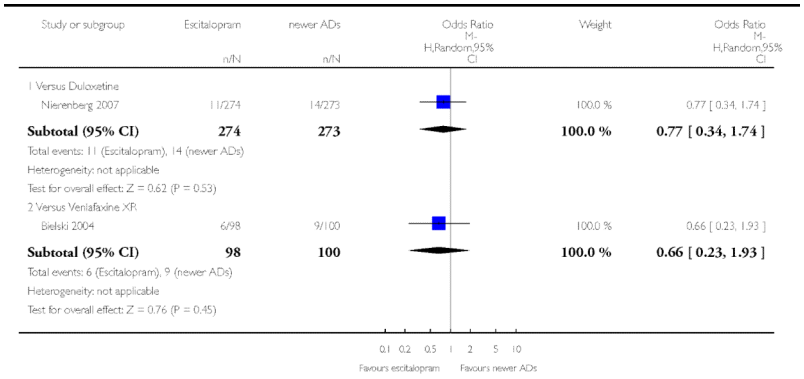
Comparison: 27 SE - Decreased libido

Outcome: 1 Escitalopram versus other SSRIs



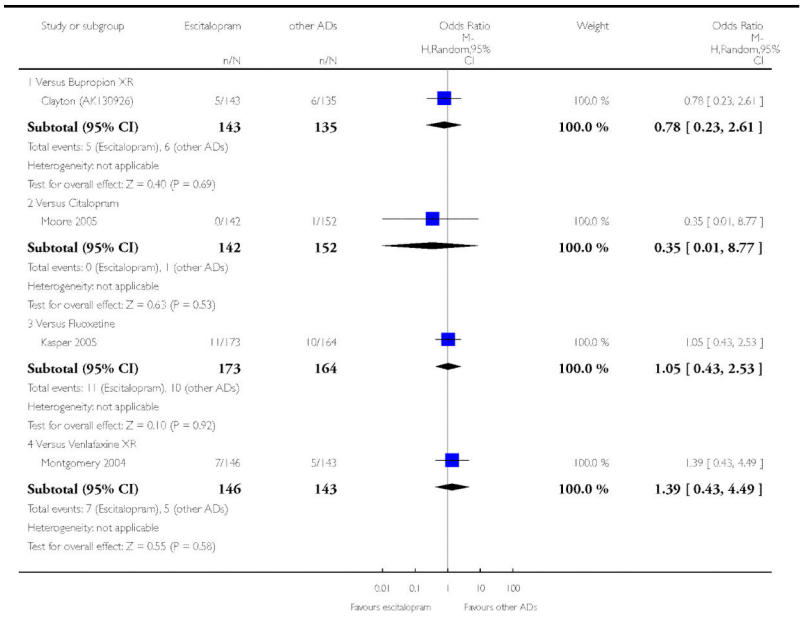
Analysis 27.2
Comparison 27 SE - Decreased libido, Outcome 2
Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 27 SE - Decreased libido
Outcome: 2 Escitalopram versus newer ADs



Analysis 28.1
Comparison 28 SE - Pain, Outcome 1 Abdominal Pain

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 28 SE - Pain
Outcome: 1 Abdominal Pain

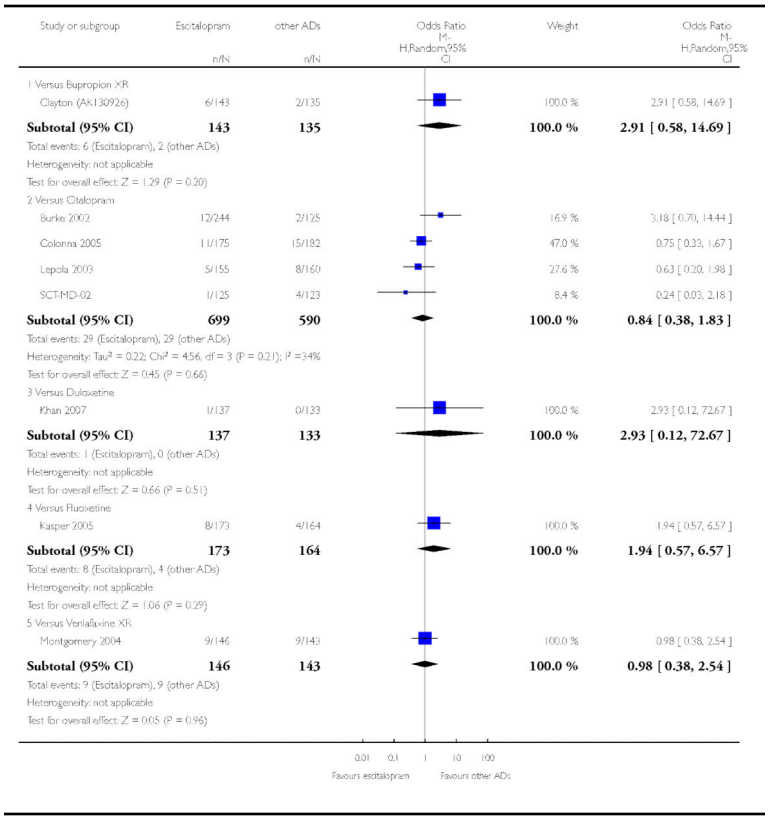


Analysis 28.2
Comparison 28 SE - Pain, Outcome 2 Back Pain

Review: Escitalopram versus other antidepressive agents for depression

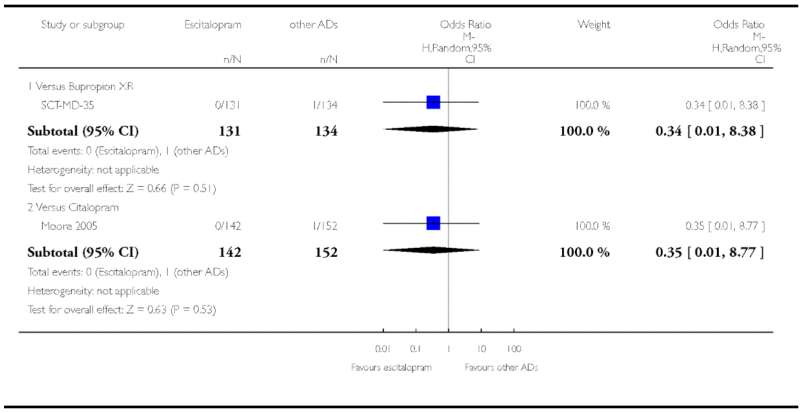
Comparison: 28 SE - Pain

Outcome: 2 Back Pain



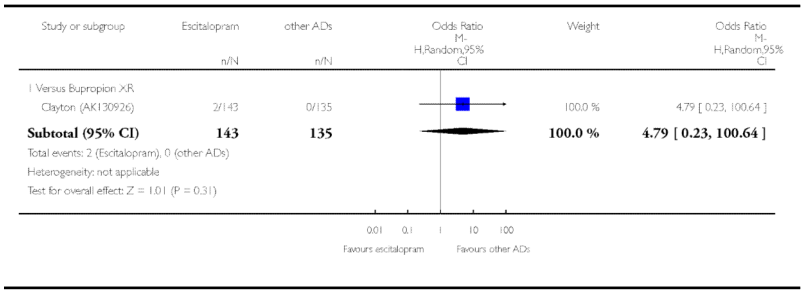
Analysis 28.3
Comparison 28 SE - Pain, Outcome 3 Chest Pain

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 28 SE - Pain
Outcome: 3 Chest Pain



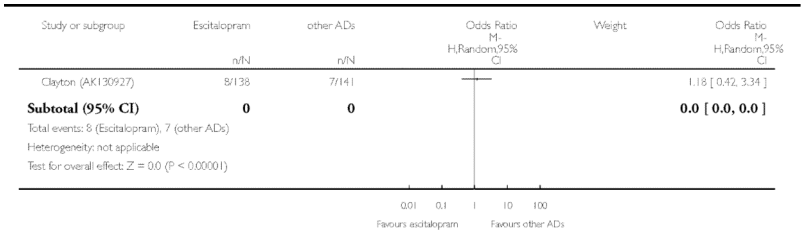
Analysis 28.4
Comparison 28 SE - Pain, Outcome 4 Pain In Extremity

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 28 SE - Pain
Outcome: 4 Pain In Extremity



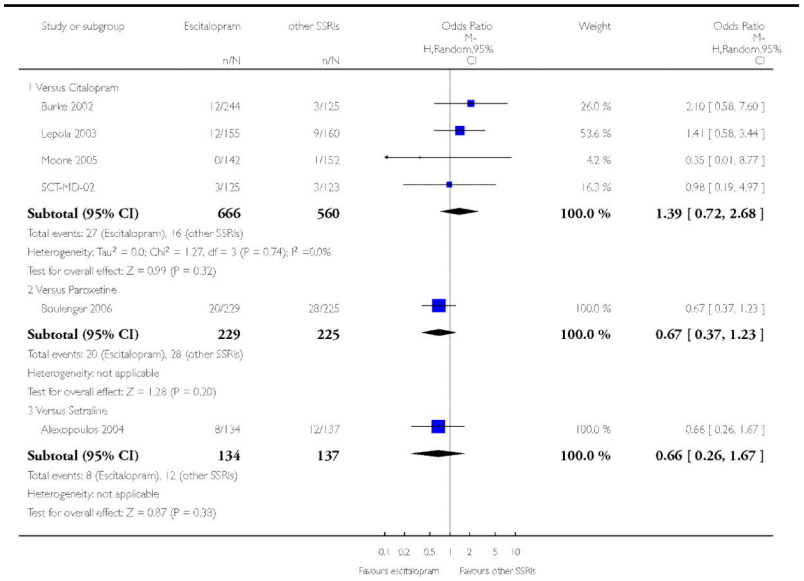
Analysis 28.5
Comparison 28 SE - Pain, Outcome 5
Pharyngolaryngeal Pain

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 28 SE - Pain
Outcome: 5 Pharyngolaryngeal Pain



Analysis 29.1
Comparison 29 SE - Increased sweating, Outcome 1
Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 29 SE - Increased sweating
Outcome: 1 Escitalopram versus other SSRIs



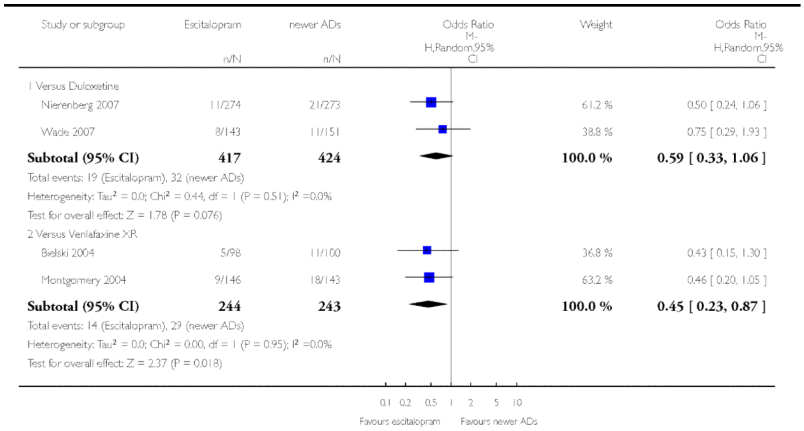
Analysis 29.2

Comparison 29 SE - Increased sweating, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 29 SE - Increased sweating

Outcome: 2 Escitalopram versus newer ADs



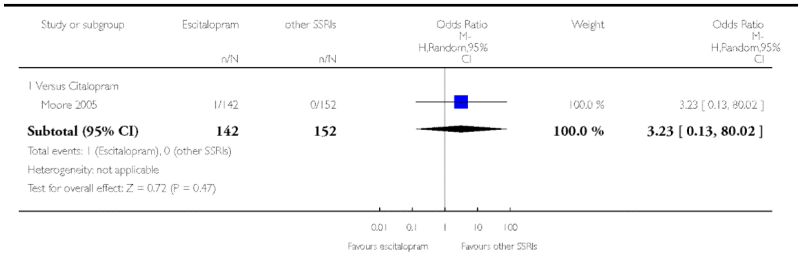
Analysis 30.1

Comparison 30 SE - Yawning, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

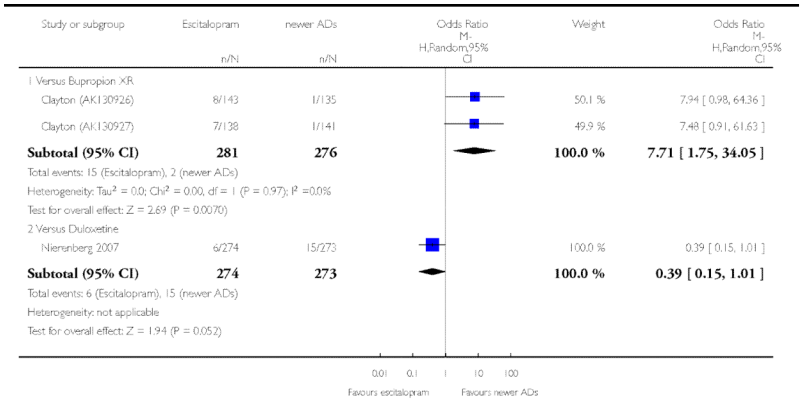
Comparison: 30 SE - Yawning

Outcome: 1 Escitalopram versus other SSRIs



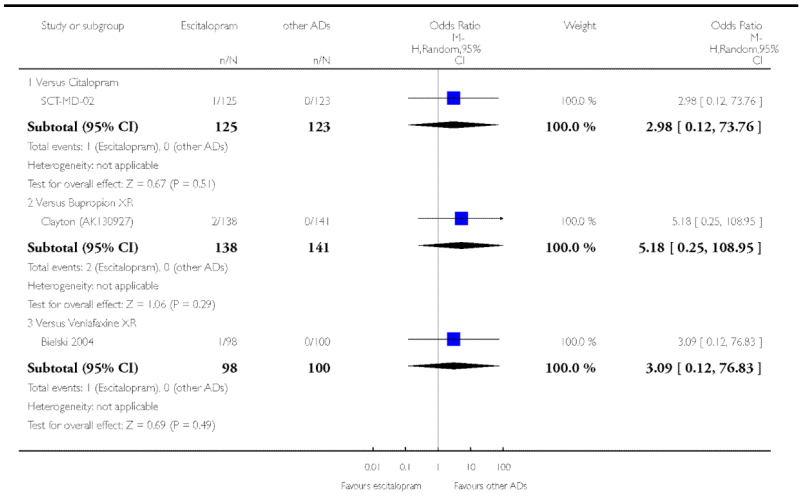
Analysis 30.2
Comparison 30 SE - Yawning, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 30 SE - Yawning
Outcome: 2 Escitalopram versus newer ADs



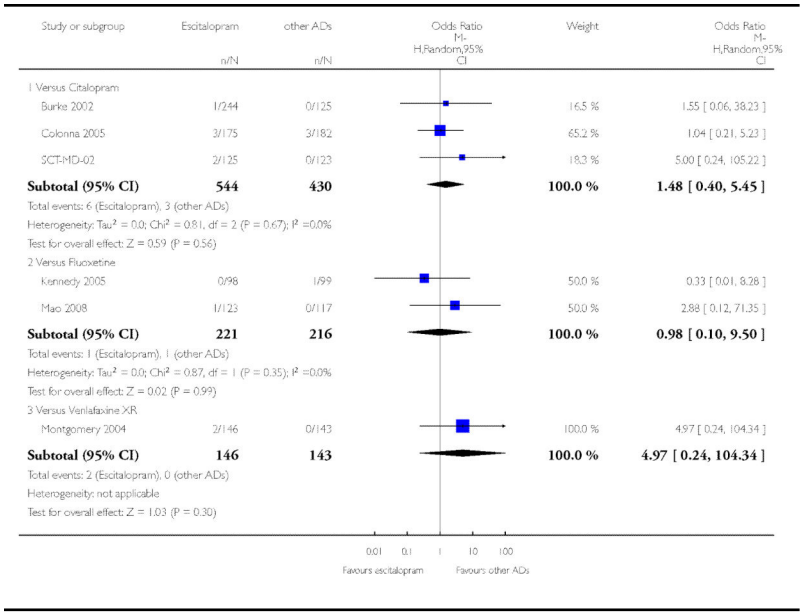
Analysis 31.1
Comparison 31 Deaths, suicide and suicidality, Outcome 1 Suicide - Tendency/Ideation

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 31 Deaths, suicide and suicidality
Outcome: 1 Suicide - Tendency/Ideation



Analysis 31.2
Comparison 31 Deaths, suicide and suicidality, Outcome 2 Suicide - Attempted

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 31 Deaths, suicide and suicidality
Outcome: 2 Suicide - Attempted



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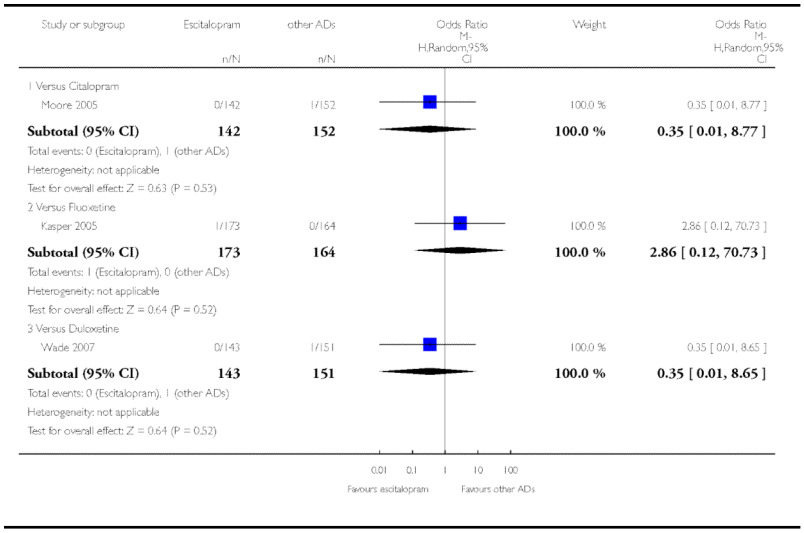
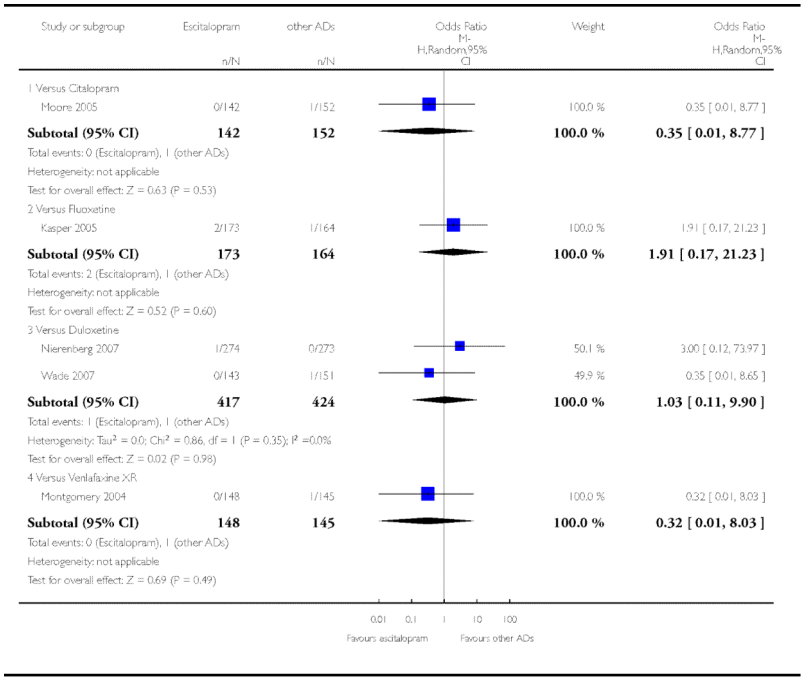
Analysis 31.3
Comparison 31 Deaths, suicide and suicidality, Outcome 3 Suicide - Completed

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 31 Deaths, suicide and suicidality
Outcome: 3 Suicide - Completed



Analysis 31.4
Comparison 31 Deaths, suicide and suicidality, Outcome 4 Deaths

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 31 Deaths, suicide and suicidality
Outcome: 4 Deaths



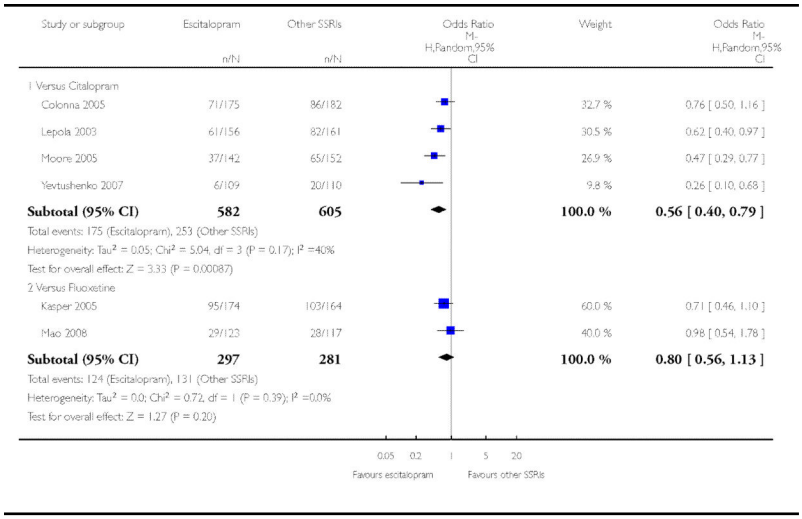
Analysis 32.1

Comparison 32 Sensitivity analyses - Excluding trials whose dropout rate was greater than 20%, Outcome 1 Escitalopram versus other SSRIs (dropout rate greater than 20% in both arms)

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 32 Sensitivity analyses - Excluding trials whose dropout rate was greater than 20%

Outcome: 1 Escitalopram versus other SSRIs (dropout rate greater than 20% in both arms)



Europe PMC Funders Author Manuscripts

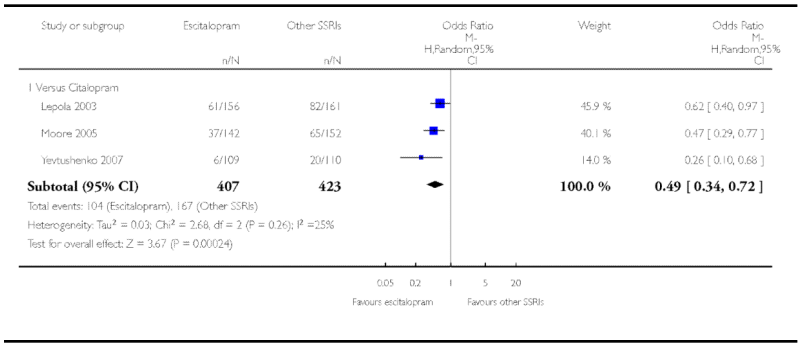
Analysis 32.2

Comparison 32 Sensitivity analyses - Excluding trials whose dropout rate was greater than 20%, Outcome 2 Escitalopram versus other SSRIs (dropout rate greater than 20% in only one arm)

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 32 Sensitivity analyses - Excluding trials whose dropout rate was greater than 20%

Outcome: 2 Escitalopram versus other SSRIs (dropout rate greater than 20% in only one arm)



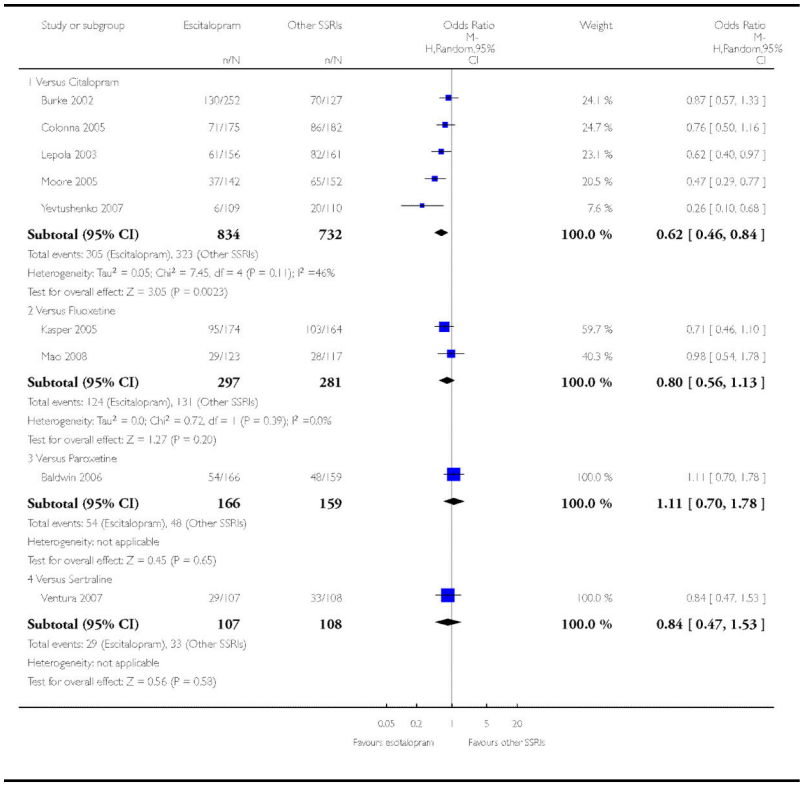
Analysis 33.1

Comparison 33 Sensitivity analyses - Excluding trials for which the imputation methods were used - RESPONSE, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 33 Sensitivity analyses - Excluding trials for which the imputation methods were used - RESPONSE

Outcome: 1 Escitalopram versus other SSRIs



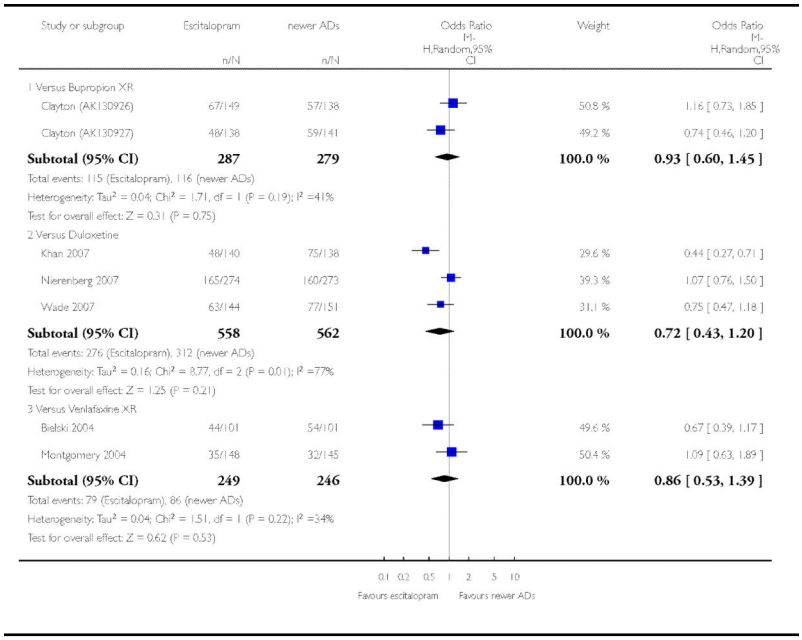
Analysis 33.2

Comparison 33 Sensitivity analyses - Excluding trials for which the imputation methods were used - RESPONSE, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 33 Sensitivity analyses - Excluding trials for which the imputation methods were used - RESPONSE

Outcome: 2 Escitalopram versus newer ADs



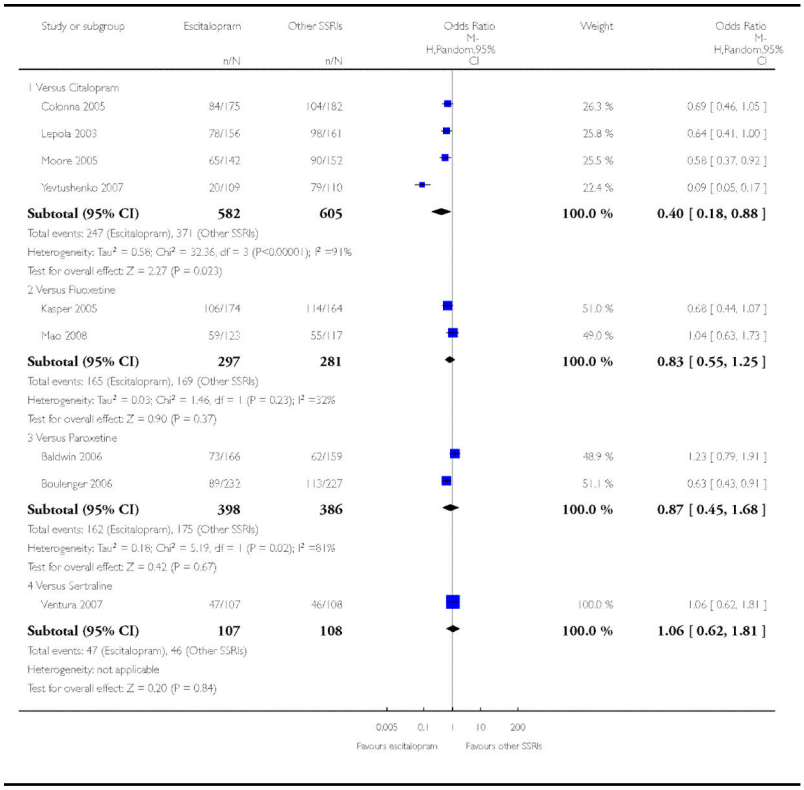
Analysis 34.1

Comparison 34 Sensitivity analyses - Excluding trials for which the imputation methods were used - REMISSION, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 34 Sensitivity analyses - Excluding trials for which the imputation methods were used - REMISSION

Outcome: 1 Escitalopram versus other SSRIs



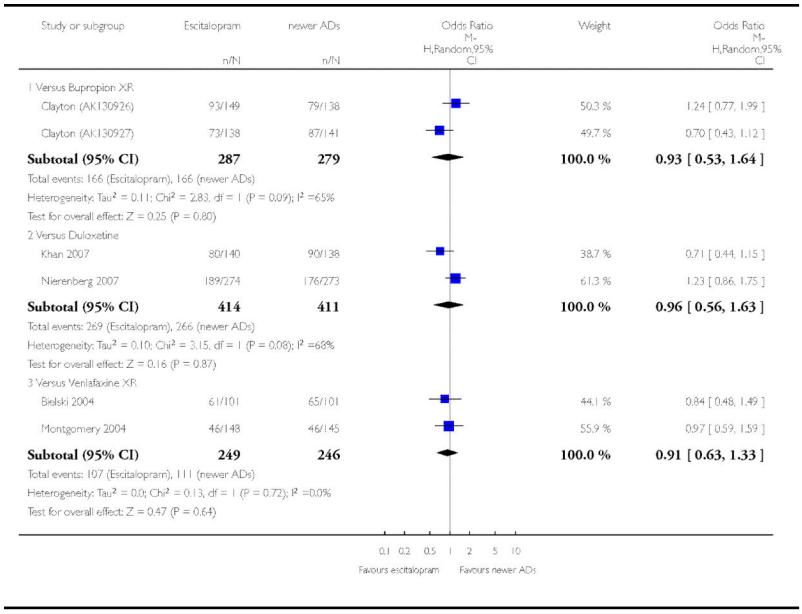
Analysis 34.2

Comparison 34 Sensitivity analyses - Excluding trials for which the imputation methods were used - REMISSION, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 34 Sensitivity analyses - Excluding trials for which the imputation methods were used - REMISSION

Outcome: 2 Escitalopram versus newer ADs



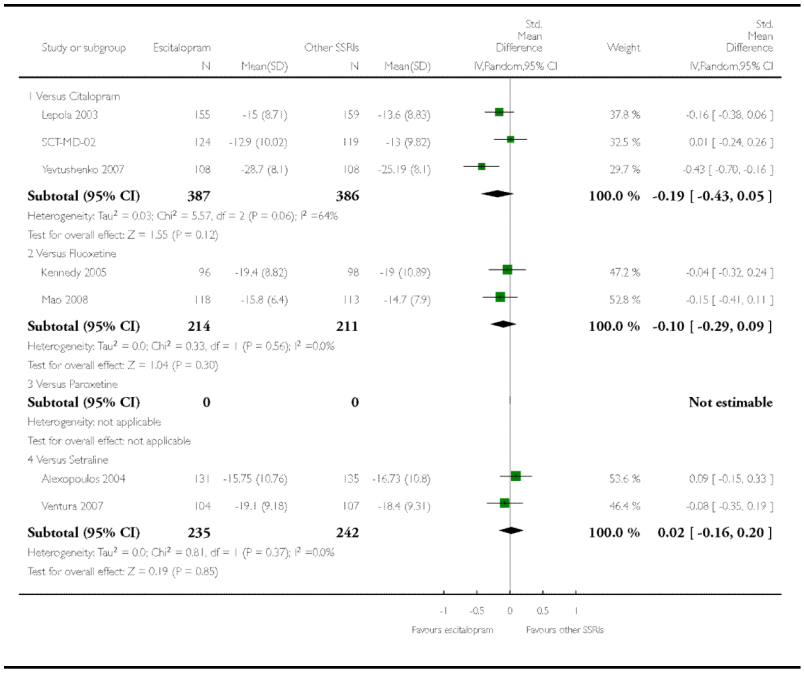
Analysis 35.1

Comparison 35 Sensitivity analyses - Excluding trials for which the imputation methods were used - STANDARD DEVIATION, Outcome 1 Escitalopram versus other SSRIs

Review: Escitalopram versus other antidepressive agents for depression

Comparison: 35 Sensitivity analyses - Excluding trials for which the imputation methods were used - STANDARD DEVIATION

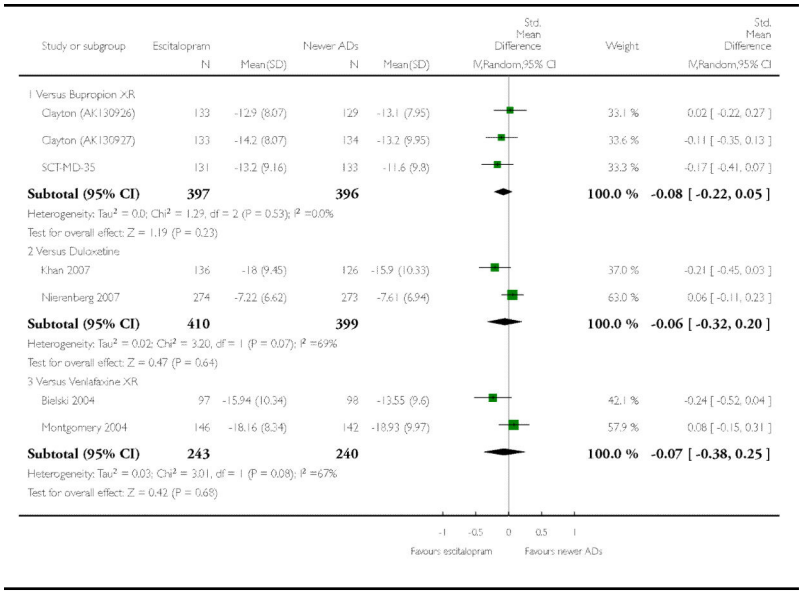
Outcome: 1 Escitalopram versus other SSRIs



Analysis 35.2

Comparison 35 Sensitivity analyses - Excluding trials for which the imputation methods were used - STANDARD DEVIATION, Outcome 2 Escitalopram versus newer ADs

Review: Escitalopram versus other antidepressive agents for depression
Comparison: 35 Sensitivity analyses - Excluding trials for which the imputation methods were used - STANDARD DEVIATION
Outcome: 2 Escitalopram versus newer ADs



WHAT'S NEW

Last assessed as up-to-date: 31 May 2008.

Date	Event	Description
13 May 2009	Amended	Contact details changed

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 2, 2009

Date	Event	Description
10 July 2008	Amended	Converted to new review format and last update of the search
13 March 2007	New citation required and conclusions have changed	Substantive amendment

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.

References to studies included in this review

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Clayton (AK130927) {published and unpublished data} . www.gsk.com/research/clinical/clinicalreg.html

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Escitalopram versus other antidepressive agents for depression

Although pharmacological and psychological interventions are both effective for major depression, antidepressant drugs remain the mainstay of treatment. During the last 20 years, selective serotonin reuptake inhibitors (SSRIs) have progressively become the most commonly prescribed antidepressants. Escitalopram, the last SSRI introduced in the market, is the pure S-enantiomer of the racemic citalopram. In the present review we assessed the evidence for the efficacy, acceptability and tolerability of escitalopram in comparison with all other antidepressants in the acute-phase treatment of major depression. Twenty-two randomised controlled trials (about 4000 participants) were included in the present review. Escitalopram appears to be suitable as first-line antidepressant treatment for people with moderate to severe major depression. It has been compared with only a few other antidepressants and so we are unable to say whether it is better, worse or the same as many of the other drugs used in practice. However, it did perform better than citalopram when we brought together the results of six studies in nearly two thousand patients

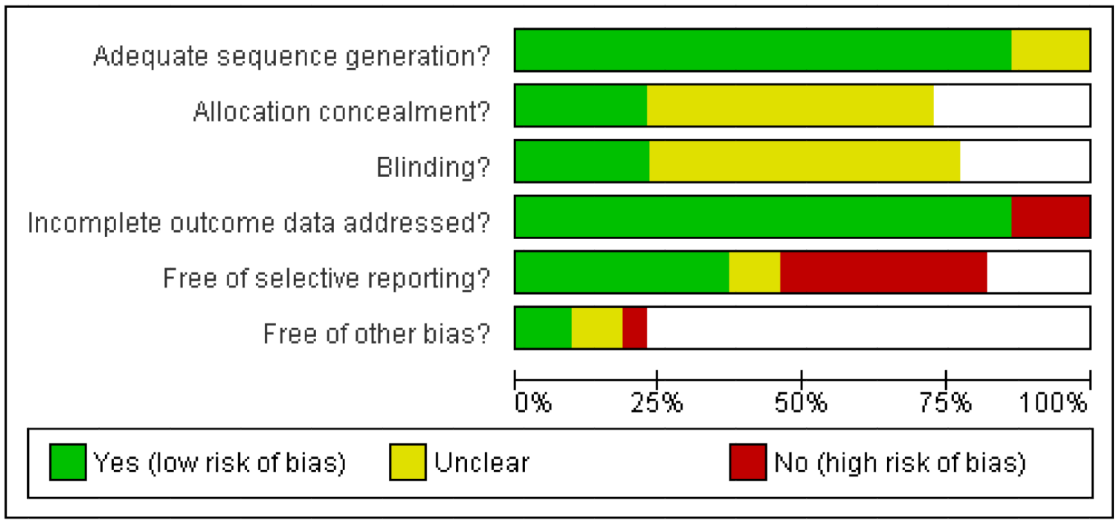

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

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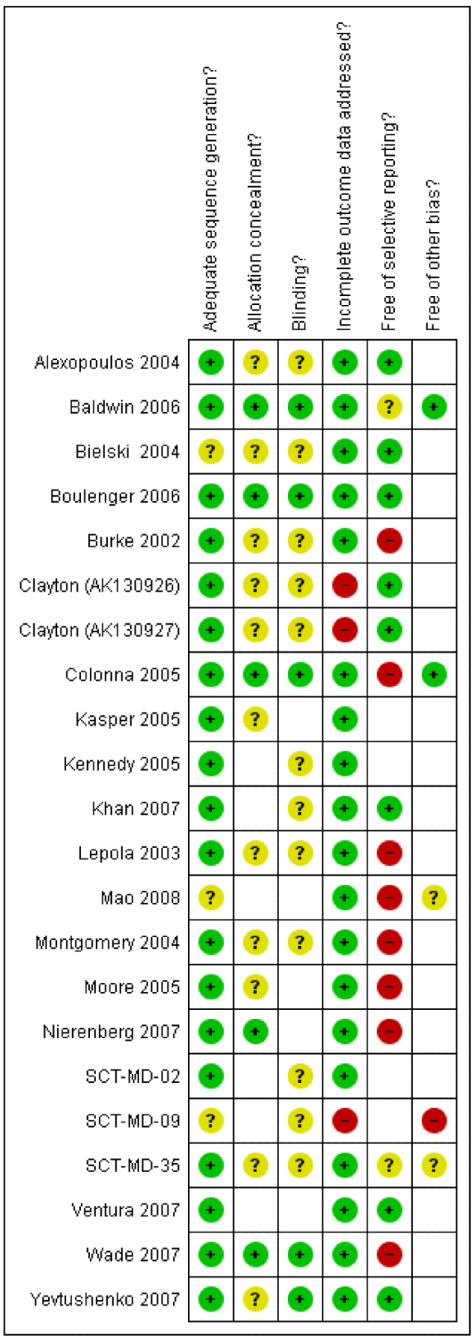

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

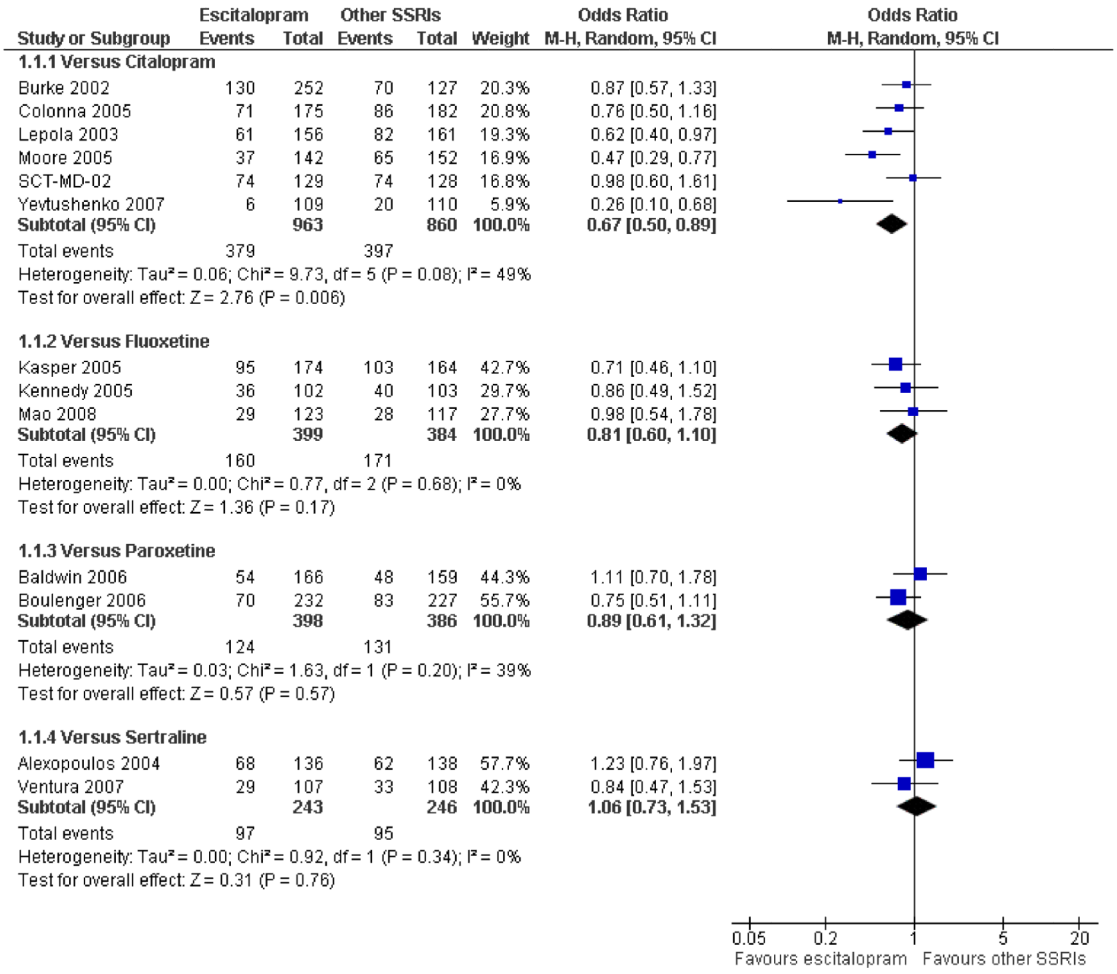

Figure 3. Forest plot of comparison: 1 Failure to respond at endpoint (6-12 weeks), outcome: 1.1 Escitalopram versus other SSRIs

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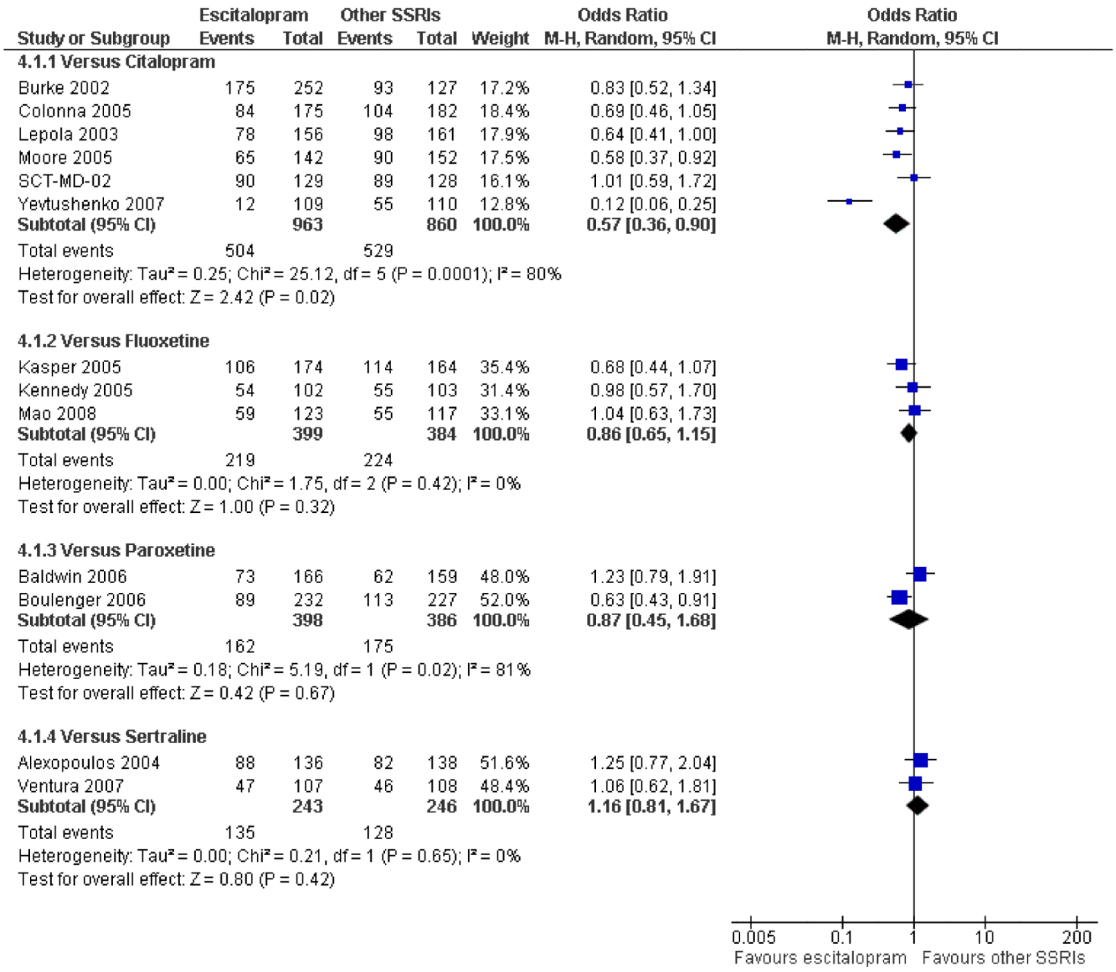

Figure 4. Forest plot of comparison: 4 Failure to remission at endpoint (6-12 weeks), outcome: 4.1 Escitalopram versus other SSRIs

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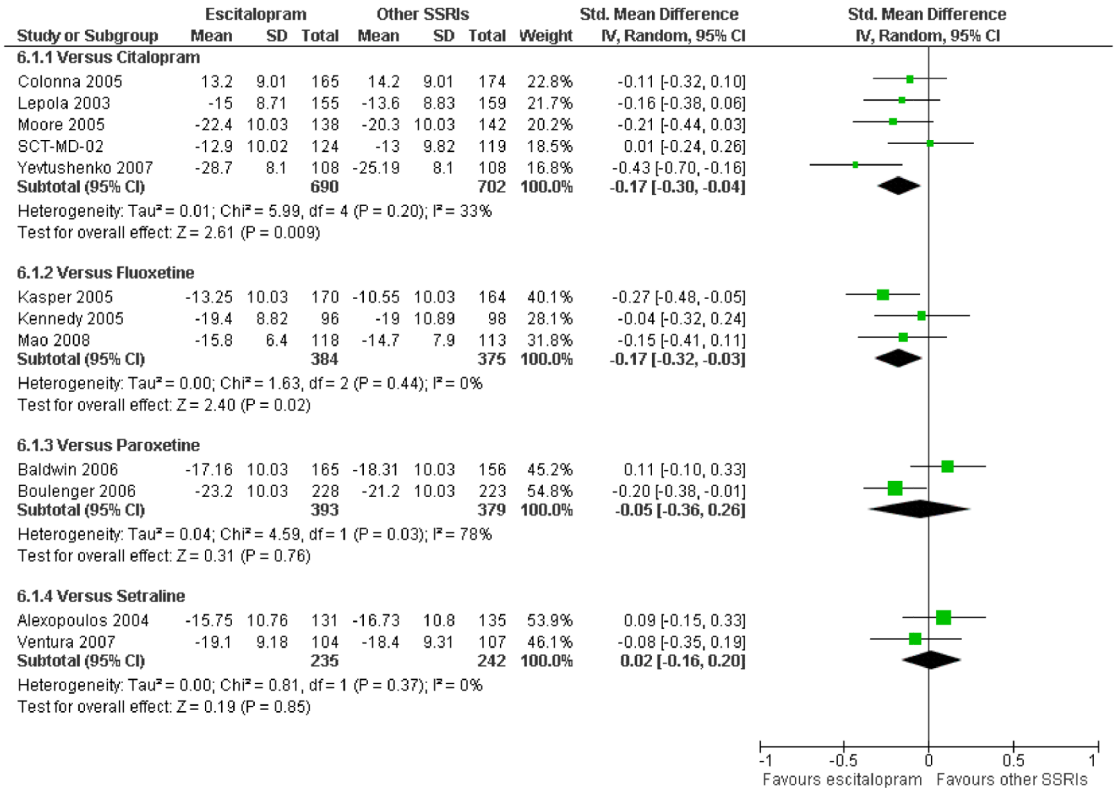

Figure 5. Forest plot of comparison: 6 Standardised mean difference at endpoint (6-12 weeks), outcome: 6.1 Escitalopram versus other SSRIs

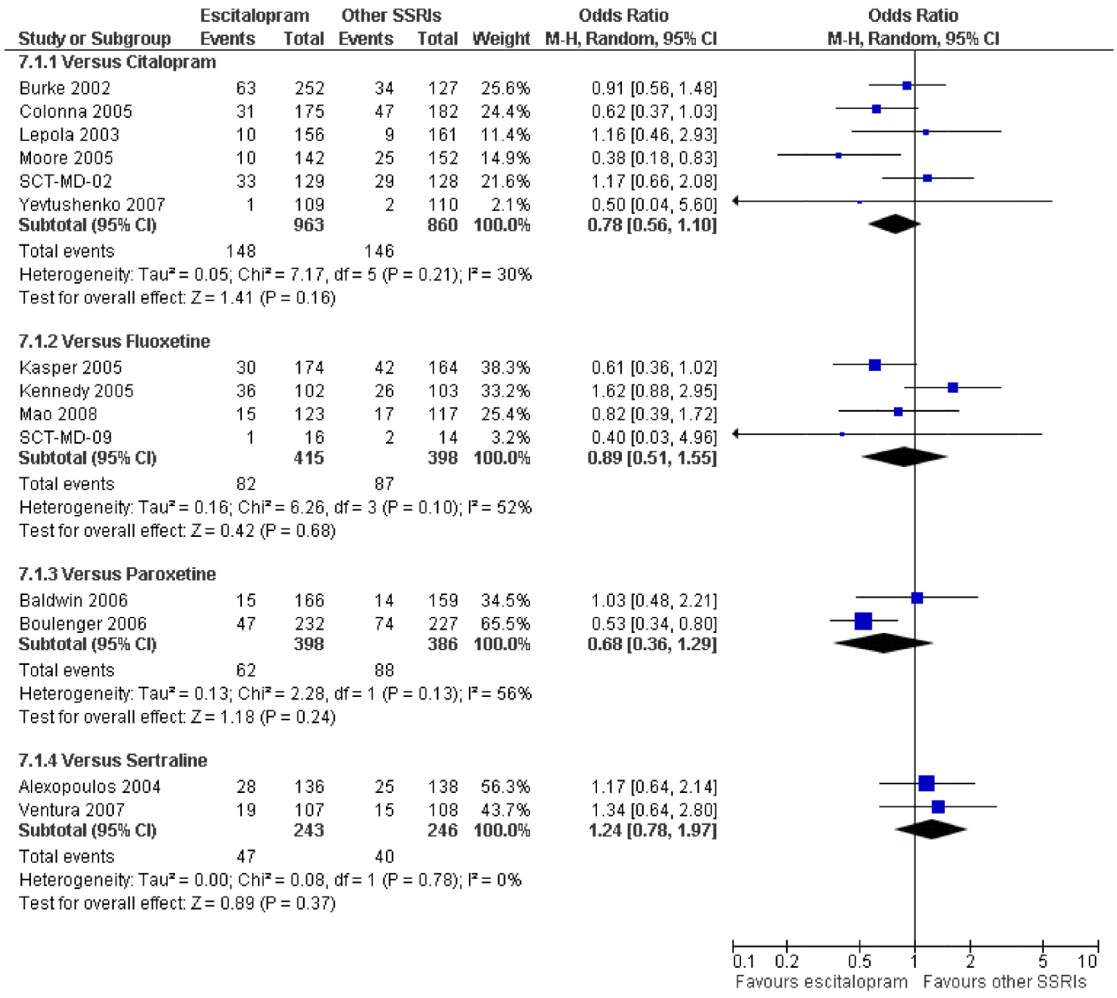

Figure 6. Forest plot of comparison: 7 Failure to complete (any cause), outcome: 7.1 Escitalopram vs. other SSRIs

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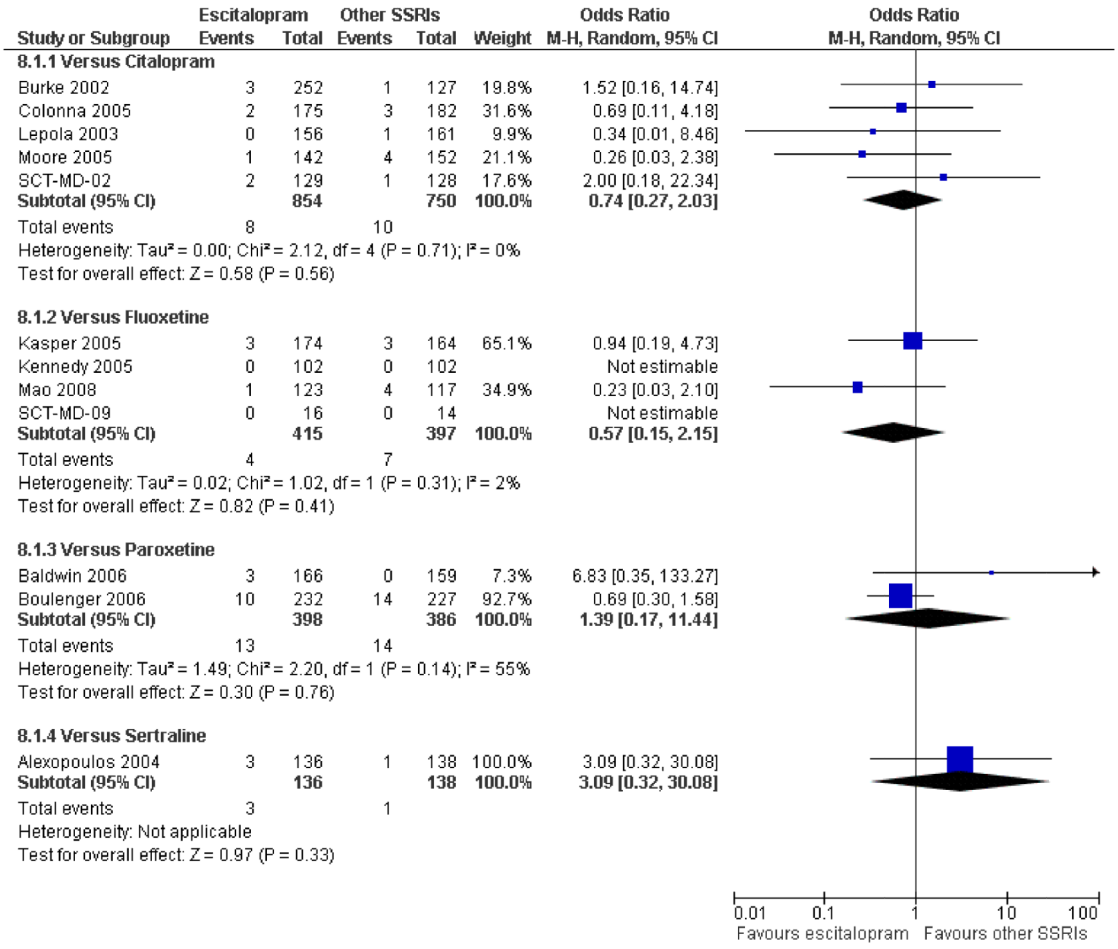

Figure 7. Forest plot of comparison: 8 Failure to complete (due to inefficacy), outcome: 8.1 Escitalopram versus other SSRIs

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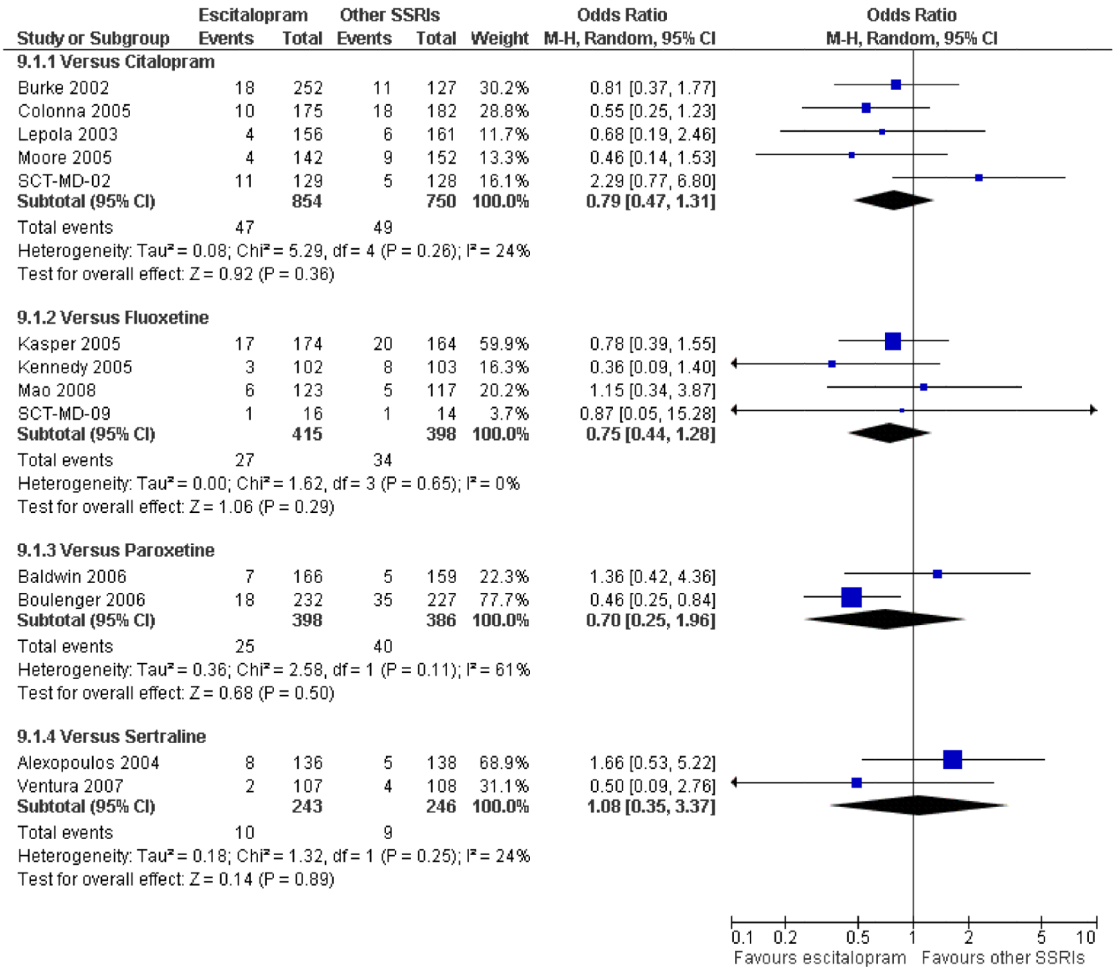

Figure 8. Forest plot of comparison: 9 Failure to complete (due to side effects), outcome: 9.1 Escitalopram vs. other SSRIs

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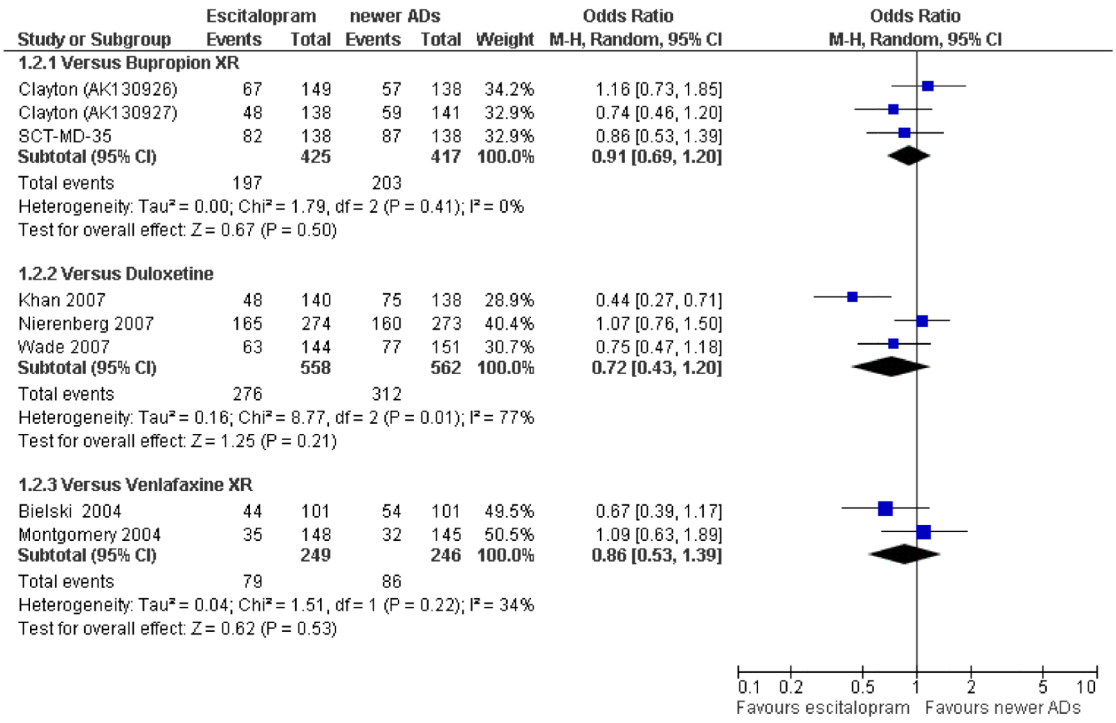

Figure 9. Forest plot of comparison: 1 Failure to respond at endpoint (6-12 weeks), outcome: 1.2 Escitalopram versus newer ADs

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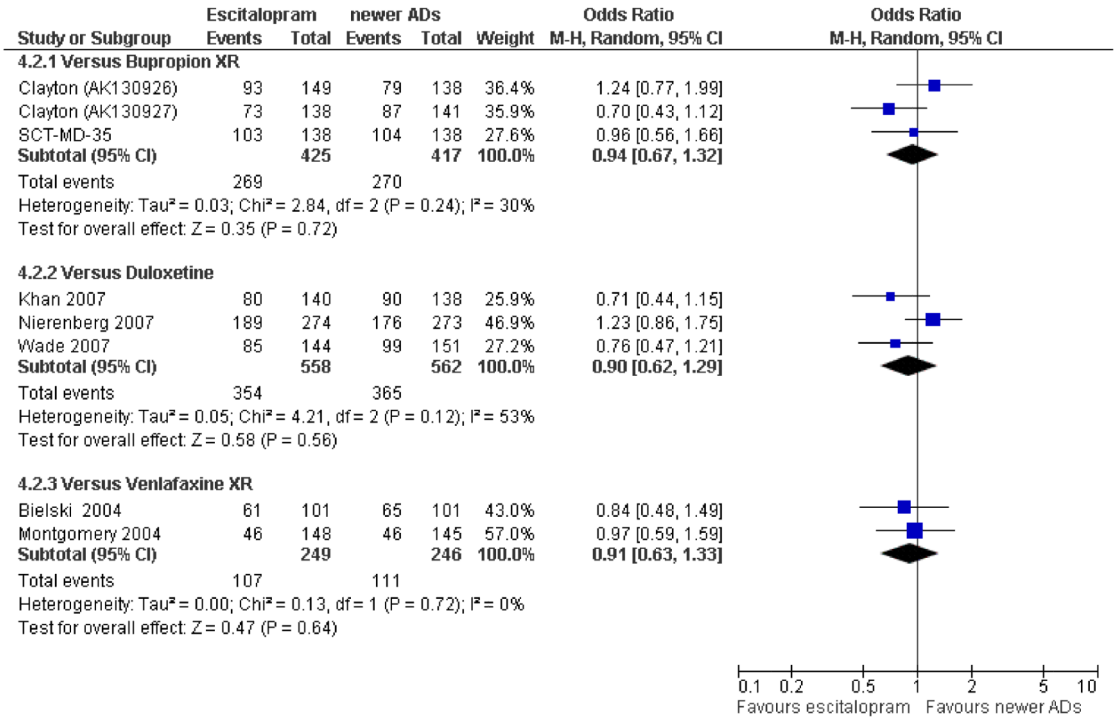

Figure 10. Forest plot of comparison: 4 Failure to remission at endpoint (6-12 weeks), outcome: 4.2 Escitalopram versus newer ADs

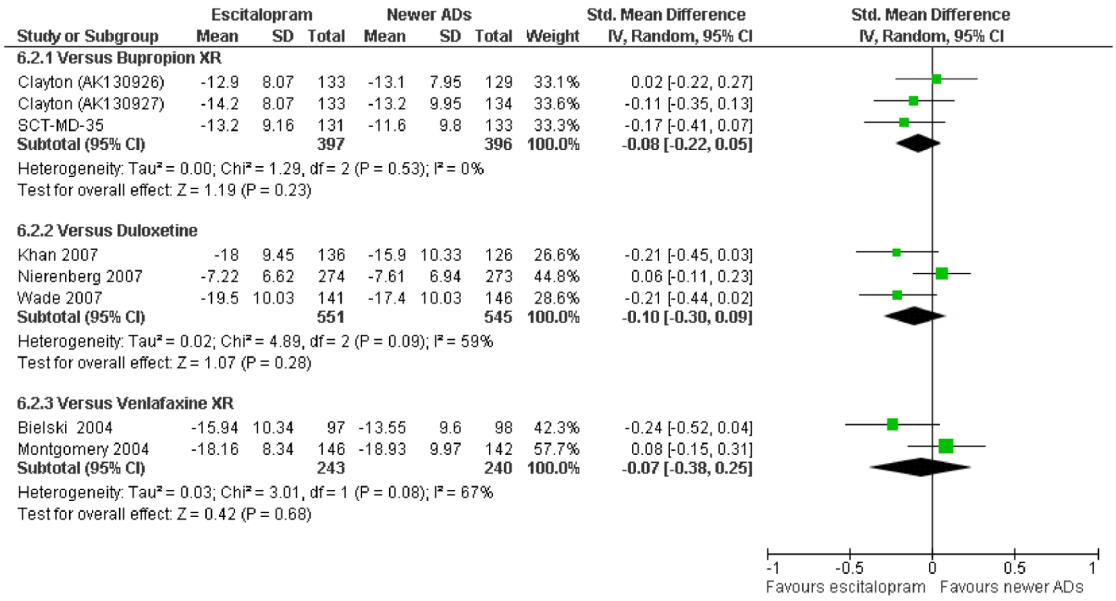

Figure 11. Forest plot of comparison: 6 Standardised mean difference at endpoint (6-12 weeks), outcome: 6.2 Escitalopram versus newer ADs

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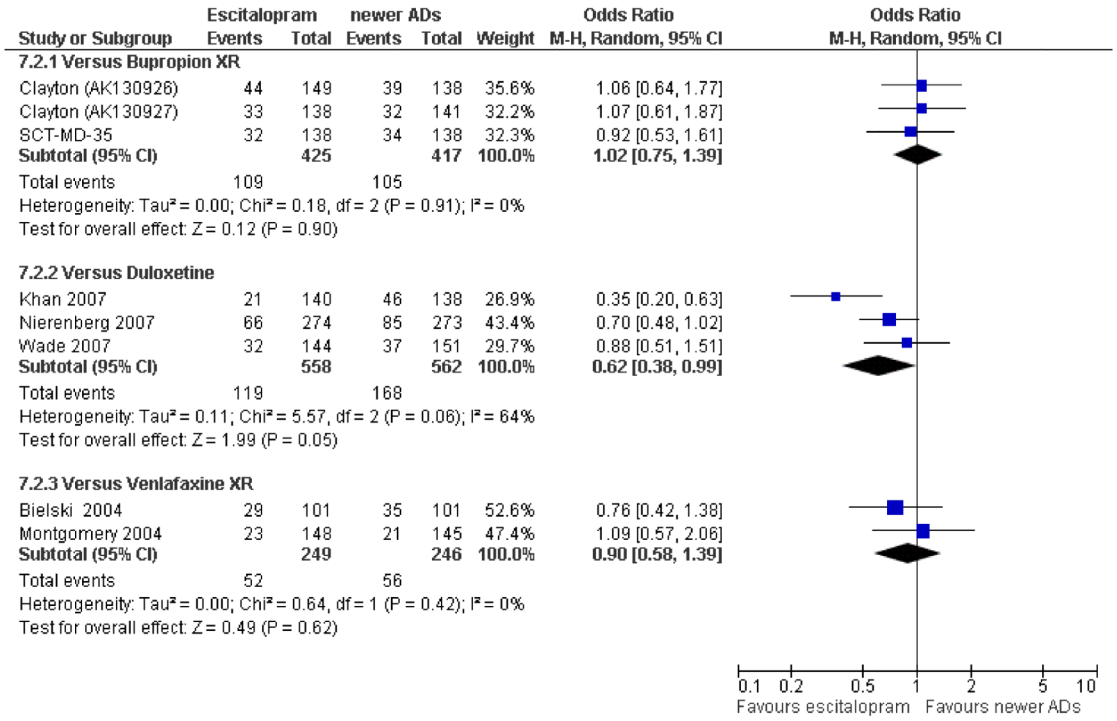

Figure 12. Forest plot of comparison: 7 Failure to complete (any cause), outcome: 7.2 Escitalopram versus newer ADs

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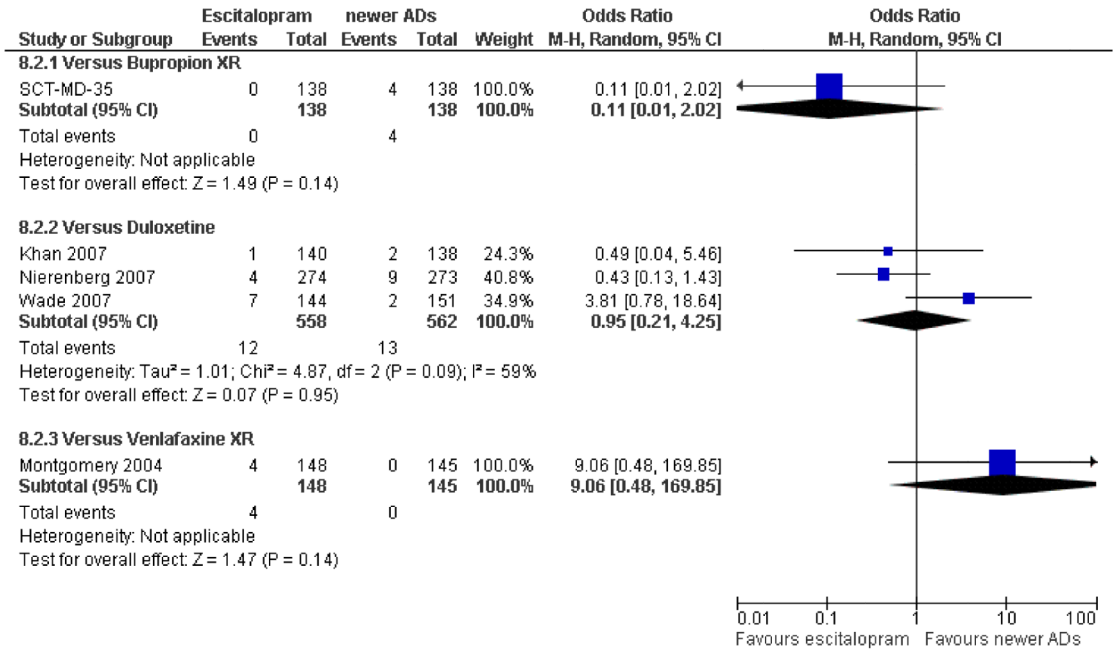

Figure 13. Forest plot of comparison: 8 Failure to complete (due to inefficacy), outcome: 8.2 Escitalopram versus newer ADs

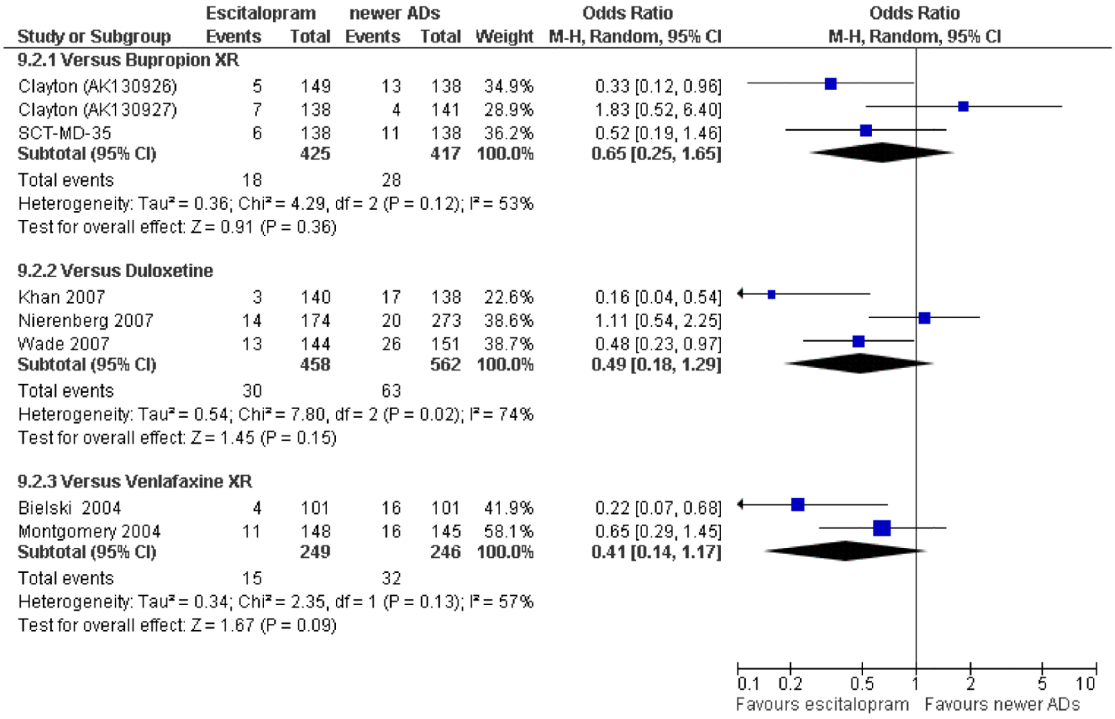

Figure 14. Forest plot of comparison: 9 Failure to complete (due to side effects), outcome: 9.2 Escitalopram versus newer ADs

Table 1

Adverse events

Adverse event	Study	Escitalopram		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Escitalopram versus citalopram						
Accidental overdose	Burke 2002	0	244	1	125	0.17 [0.01, 4.20]
Aggressive behaviour	Moore 2005	1	142	0	152	3.23 [0.13, 80.02]
Anaphylaxis	Burke 2002	1	244	0	125	1.55 [0.06, 38.23]
Anorexia	Yevtushenko 2007	0	108	1	108	0.33 [0.01, 8.20]
Asthenia	Moore 2005	2	142	2	152	1.07 [0.15, 7.71]
Bronchitis	Colonna 2005, Lepola 2003	13	330	11	342	1.24 [0.54, 2.83]
Coma	Burke 2002	0	244	1	125	0.17 [0.01, 4.20]
Concentration decrease	Moore 2005	0	142	1	152	0.35 [0.01, 8.77]
Death fetal	Lepola 2003	0	116	1	111	0.32 [0.01, 7.84]
Dehydration	SCT-MD-02	0	125	1	123	0.33 [0.01, 8.06]
Depression	Moore 2005	0	142	1	152	0.35 [0.01, 8.77]
Dermatological problems	Moore 2005, Yevtushenko 2007	1	250	3	260	0.44 [0.06, 3.02]
Disease Of Liver And Hepatic Duct	SCT-MD-02	0	125	1	123	0.33 [0.01, 8.06]
Dizziness	Burke 2002, Moore 2005, SCT-MD-02	31	511	15	400	1.43 [0.58, 3.49]
Dyspepsia	Yevtushenko 2007	0	108	1	108	0.33 [0.01, 8.20]
Enuresis	Moore 2005	1	142	0	152	3.23 [0.13, 80.02]
Forgetfulness	Moore 2005	0	142	2	152	0.21 [0.01, 4.44]
Hot flashes	Moore 2005	1	142	0	152	3.23 [0.13, 80.02]
Inflicted injury	Burke 2002	8	244	3	125	1.38 [0.36, 5.29]
Non-accidental overdose	SCT-MD-02	1	125	0	123	2.98 [0.12, 73.76]
Ophtalmological problems	Moore 2005	0	142	2	152	0.21 [0.01, 4.44]
Oppression	Moore 2005	0	142	1	152	0.35 [0.01, 8.77]
Palpitation	Moore 2005	1	142	0	152	3.23 [0.13, 80.02]
Panic attack	Moore 2005	0	142	1	152	0.35 [0.01, 8.77]
Pelvic inflammation	Lepola 2003	1	116	0	111	2.90 [0.12, 71.85]
Pharyngitis	Burke 2002, Lepola 2003, Moore 2005	18	541	12	437	0.92 [0.41, 2.06]
Pregnancy unintended	Lepola 2003	1	116	0	111	2.90 [0.12, 71.85]
Rhinitis	Burke 2002, Colonna 2005, Lepola 2003, SCT-MD-02	46	699	33	590	1.19 [0.73, 1.91]
Sexual problems	Burke 2002, Lepola 2003, SCT-MD-02, Yevtushenko 2007	19	283	15	267	1.14 [0.53, 2.44]
Sinusitis	Lepola 2003	6	155	4	160	1.57 [0.43, 5.68]
Subjects with non-fatal severe adverse events	Burke 2002, Lepola 2003, SCT-MD-02	6	524	4	408	1.12 [0.31, 4.08]
Tachycardia	SCT-MD-02	1	125	0	123	2.98 [0.12, 73.76]

Adverse event	Study	Escitalopram		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Tinnitus	Moore 2005	0	142	1	152	0.35 [0.01, 8.77]
Tremor	Moore 2005	3	142	0	152	7.65 [0.39, 149.47]
Trismus	Moore 2005	0	142	1	152	0.35 [0.01, 8.77]
Upper respiratory tract infection	Burke 2002, Lepola 2003, SCT-MD-02	31	524	16	408	1.59 [0.85, 2.98]
Weight gain	Colonna 2005, Moore 2005	4	317	14	334	0.38 [0.06, 2.37]
Escitalopram versus bupropion XR						
Accidental overdose	Clayton (AK130926)	0	143	1	135	0.31 [0.01, 7.74]
Decreased appetite	Clayton (AK130927)	13	138	9	141	1.53 [0.63, 3.69]
Disease Of Liver And Hepatic Duct	Clayton (AK130927) , SCT-MD-35	2	269	0	275	3.09 [0.32, 29.89]
DIzziness	Clayton (AK130926) , Clayton (AK130927)	15	281	18	276	0.84 [0.33, 2.12]
Dyspepsia	Clayton (AK130926)	5	143	5	135	0.94 [0.27, 3.33]
Flatulence	Clayton (AK130926)	8	143	4	135	1.94 [0.57, 6.60]
Irritability	Clayton (AK130926) , Clayton (AK130927)	3	281	14	276	0.26 [0.06, 1.04]
Musculoskeletal disorder	SCT-MD-35	10	131	9	134	1.15 [0.45, 2.92]
Nasal congestion	Clayton (AK130926), Clayton (AK130927)	11	281	6	276	1.86 [0.68, 5.11]
Non-accidental overdose	Clayton (AK130927)	1	138	0	141	3.09 [0.12, 76.44]
Palpitation	Clayton (AK130926)	3	143	4	135	0.70 [0.15, 3.20]
Pharyngitis	Clayton (AK130927)	7	138	9	141	0.78 [0.28, 2.17]
Subjects with non-fatal severe adverse events	Clayton (AK130926) , Clayton (AK130927) , SCT-MD-35	5	410	5	412	0.95 [0.24, 3.72]
Tooth ache	Clayton (AK130926)	3	143	2	135	1.43 [0.23, 8.66]
Tremor	Clayton (AK130926)	3	143	6	135	0.46 [0.11, 1.88]
Upper respiratory tract infection	Clayton (AK130926) , SCT-MD-35	20	274	14	269	1.45 [0.68, 3.08]
Escitalopram versus duloxetine						
Accidental overdose	Khan 2007	0	137	1	133	0.32 [0.01, 7.96]
Chest pressure	Khan 2007	0	137	1	133	0.32 [0.01, 7.96]
Decreased appetite	Nierenberg 2007	13	274	22	273	0.57 [0.28, 1.15]
Depression	Khan 2007	0	137	2	133	0.19 [0.01, 4.02]
Dizziness	Khan 2007, Nierenberg 2007, Wade 2007	39	554	64	557	0.59 [0.39, 0.90]
Dyspepsia	Wade 2007	9	143	4	151	2.47 [0.74, 8.20]
Hypertension	Khan 2007	0	137	1	133	0.32 [0.01, 7.96]
Musculoskeletal disorder	Khan 2007	18	137	12	133	1.53 [0.70, 3.30]
Pharyngitis	Wade 2007	15	143	11	151	1.49 [0.66, 3.37]
Sexual problems	Khan 2007	5	56	7	48	0.57 [0.17, 1.94]

Adverse event	Study	Escitalopram		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Subjects with non-fatal severe adverse events	Khan 2007, Nierenberg 2007	4	411	9	406	0.45 [0.07, 2.80]
Upper respiratory tract infection	Khan 2007, Nierenberg 2007	57	411	48	406	1.21 [0.79, 1.85]
Escitalopram versus fluoxetine						
Anorexia	Kasper 2005	2	173	4	164	0.47 [0.08, 2.59]
Depression	Kasper 2005	2	173	4	164	0.47 [0.08, 2.59]
Dermatological problems	SCT-MD-09	3	16	2	14	1.38 [0.20, 9.77]
Disease Of Liver And Hepatic Duct	Mao 2008	2	123	6	117	0.31 [0.06, 1.55]
DIzziness	Kasper 2005, Kennedy 2005, Mao 2008	20	394	22	380	0.88 [0.46, 1.67]
Dyspepsia	Kasper 2005	4	173	7	164	0.53 [0.15, 1.85]
Hypertension	Kasper 2005	4	173	4	164	0.95 [0.23, 3.85]
Indigestion	Kennedy 2005	2	98	6	99	0.32 [0.06, 1.64]
Orthostatic symptoms	Kasper 2005	2	173	1	164	1.91 [0.17, 21.23]
Rhinitis	SCT-MD-09	1	16	3	14	0.24 [0.02, 2.68]
Sexual problems	Kennedy 2005	4	37	1	32	3.76 [0.40, 35.49]
Subjects with non-fatal severe adverse events	Kasper 2005, Kennedy 2005, Mao 2008	8	394	16	380	0.48 [0.20, 1.14]
Tooth ache	SCT-MD-09	1	16	2	14	0.40 [0.03, 4.96]
Vertigo	Kasper 2005	3	173	7	164	0.40 [0.10, 1.56]
Escitalopram versus paroxetine						
DIzziness	Boulenger 2006	21	229	20	225	1.03 [0.54, 1.97]
Erectile dysfunction	Boulenger 2006	4	75	4	68	0.90 [0.22, 3.75]
Sexual problems	Boulenger 2006	2	75	6	68	0.28 [0.06, 1.45]
Subjects with non-fatal severe adverse events	Boulenger 2006	7	229	3	225	2.33 [0.60, 9.14]
Escitalopram versus sertraline						
Decreased appetite	Ventura 2007	8	104	6	108	1.42 [0.47, 4.23]
Depression	Alexopoulos 2004	1	134	0	137	3.09 [0.12, 76.52]
Flatulence	Alexopoulos 2004	6	134	6	137	1.02 [0.32, 3.26]
Indigestion	Alexopoulos 2004	3	134	7	137	0.43 [0.11, 1.68]
Rhinitis	Alexopoulos 2004	6	134	7	137	0.87 [0.28, 2.66]
Sexual problems	Alexopoulos 2004, Ventura 2007	23	162	23	172	0.91 [0.48, 1.72]
Subjects with non-fatal severe adverse events	Alexopoulos 2004	3	134	1	137	3.11 [0.32, 30.32]
Upper respiratory tract infection	Alexopoulos 2004, Ventura 2007	21	238	26	245	0.82 [0.44, 1.50]
Escitalopram versus venlafaxine						
Cardiac failure	Montgomery 2004	0	146	1	143	0.32 [0.01, 8.03]
Colon Obstruction	Bielski 2004	1	98	0	100	3.09 [0.12, 76.83]
Decreased weight	Montgomery 2004	5	146	10	143	0.47 [0.16, 1.42]
Dermatological problems	Montgomery 2004	0	146	1	143	0.32 [0.01, 8.03]

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Adverse event	Study	Escitalopram		Comparator		Odds Ratio, Random [95% CI]
		Events	Total	Events	Total	
Dizziness	Montgomery 2004	7	146	8	143	0.85 [0.30, 2.41]
Gastritis	Montgomery 2004	0	146	3	143	0.14 [0.01, 2.68]
Inflicted injury	Bielski 2004	0	98	1	100	0.34 [0.01, 8.37]
Non-accidental overdose	Bielski 2004	0	98	1	100	0.34 [0.01, 8.37]
Sexual problems	Bielski 2004	2	30	12	53	0.24 [0.05, 1.18]
Subjects with non-fatal severe adverse events	Bielski 2004, Montgomery 2004	4	244	8	243	0.51 [0.14, 1.77]
Transitory Ischaemic Attack	Montgomery 2004	0	146	1	143	0.32 [0.01, 8.03]
Vertigo	Montgomery 2004	7	146	6	143	1.15 [0.38, 3.51]