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Mirtazapine versus other antidepressive agents for depression

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Abstract

Background—Mirtazapine has a unique mechanism of antidepressive action and is one of the commonly used antidepressants in clinical practice.

Objectives—The aim of the present review was to assess the evidence on the efficacy and acceptability of mirtazapine compared with other antidepressive agents in the acute-phase treatment of major depression in adults.

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CONTRIBUTIONS OF AUTHORS

All review authors contributed to the production of the protocol. NW, IMO and TAF identified studies for inclusion and checked the methodological quality of studies. NW and IMO extracted data. NW performed the analyses. NW wrote the final review, which was approved by the other authors.

DECLARATIONS OF INTEREST

NW has received research grants from the Japanese Ministry of Education, Science, Sports and Culture; and from the Japanese Ministry of the Health, Labour and Welfare. He has also received speaking fees and research funds from Asahi Kasei, Dai-Nippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Otsuka, Pfizer and Schering-Plough.

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

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Search methods—We searched the Cochrane Collaboration Depression, Anxiety and Neurosis review group's specialised register (CCDANCTR), which includes relevant randomised controlled trials from the following bibliographic databases: The Cochrane Library (all years to April 2011), EMBASE, (1980 to July 2011) MEDLINE (1950 to July 2011) and PsycINFO (1974 to July 2011). Reference lists of the reports of relevant studies were checked and experts in the field contacted. The review was not limited to English-language articles.

Selection criteria—Randomised controlled trials (RCTs) allocating participants with major depression to mirtazapine versus any other antidepressive agent.

Data collection and analysis—Two authors independently checked eligibility and extracted data on an intention-to-treat basis. The primary outcome was response to treatment. The secondary outcomes included dropouts and individual adverse events.

Meta-analyses were conducted using the random-effects model.

Main results—A total of 29 RCTs (n = 4974), mostly following up the participants for six weeks in outpatient clinics and inadequately reporting the risk of bias, were included. In comparison with tricyclic antidepressants (10 trials, n = 1553) there was no robust evidence to detect a difference between mirtazapine and tricyclics in terms of response at two weeks (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.64 to 1.13) or at the end of acute-phase treatment (at 6 to 12 weeks) (OR 0.89, 95% CI 0.72 to 1.10). In comparison with selective serotonin reuptake inhibitors (SSRIs) (12 trials, n = 2626) mirtazapine was significantly more effective at two weeks (OR 1.57, 95% CI 1.30 to 1.88) and at the end of acute-phase treatment (OR 1.19, 95% CI 1.01 to 1.39). Mirtazapine was significantly more effective than a serotonin-noradrenaline reuptake inhibitor (venlafaxine only, two trials, n = 415) at two weeks (OR 2.29, 95% CI 1.45 to 3.59) and at the end of acute-phase treatment (OR 1.53, 95% CI 1.03 to 2.25).

In terms of dropouts, there was no robust evidence to detect a difference between mirtazapine and other antidepressants. Mirtazapine was more likely to cause weight gain or increased appetite and somnolence than SSRIs but less likely to cause nausea or vomiting and sexual dysfunction.

Authors' conclusions—Some statistically significant and possibly clinically meaningful differences between mirtazapine and other antidepressive agents were found for the acute-phase treatment of major depression. Mirtazapine is likely to have a faster onset of action than SSRIs during the acute-phase treatment. Dropouts occur similarly in participants treated with mirtazapine and those treated with other antidepressants, although the adverse event profile of mirtazapine is unique.

Medical Subject Headings (MeSH)

Antidepressive Agents [therapeutic use]; Antidepressive Agents, Tricyclic [* therapeutic use]; Cyclohexanols [therapeutic use]; Depression [* drug therapy]; Mianserin [* analogs & derivatives; therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans

BACKGROUND

Description of the condition

Major depression is generally diagnosed in people with a persistent and unreactive low mood and loss of all interest and pleasure 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 of humankind, after lower respiratory infections and HIV/AIDS, in the year 2002 and accounted for 4.5% of total human suffering (WHO 2006a). Moreover, it is expected to show a rising trend during the coming 20 years (WHO 2006b). 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 2004).

Description of the intervention

Although both pharmacological and psychological interventions are effective for major depression, in primary and secondary care settings antidepressant drugs remain the mainstay of treatment (APA 2000; Ellis 2004; NICE 2004). Amongst antidepressants many different agents are available, including tricyclics (TCAs) (for example amitriptyline, amoxapine, clomipramine, desipramine, dosulepin, doxepin, imipramine, nortriptyline), monoamine oxidase inhibitors (MAOIs) (for example moclobemide, selegiline, tranylcypromine), selective serotonin reuptake inhibitors (SSRIs) (for example citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), serotonin-noradrenaline reuptake inhibitors (SNRIs) (for example venlafaxine, duloxetine, milnacipran) and other newer agents (mirtazapine, reboxetine, bupropion).

In many western countries, antidepressant consumption has risen dramatically during the last 20 years, mainly because of the increasing consumption of SSRIs and newer antidepressants that have progressively become the most commonly prescribed antidepressants (Ciuna 2004; Guaiana 2005). SSRIs are generally better tolerated than TCAs (Barbui 2000; Hotopf 1997; Steffens 1997), and there is some evidence of similar efficacy (Anderson 2000; Williams 2000). However, head-to-head comparisons provide 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 (Cipriani 2005; Puech 1997; Smith 2002).

Given that the most recently available evidence refers to the SSRIs as a homogeneous group (Arroll 2005; Hansen 2005), it is still unclear how each of the SSRIs or newer agents compare with other antidepressants in terms of effects and side effects.

How the intervention might work

Mirtazapine is a prescription only antidepressant introduced in 1996. It has a unique pharmacological profile, including potent antagonism of central alpha 2-adrenergic autoreceptors and heteroreceptors and antagonism of both serotonin 5-hydroxytryptamine-2 (5-HT2) and 5-HT3 receptors (Kent 2000). Unlike venlafaxine and nefazodone, mirtazapine

has minimum effects on monoamine reuptake and is classified as a NaSSA (noradrenergic and specific serotonergic antidepressant). Antagonism of alpha 2-adrenergic receptors leads to blockade of presynaptic autoreceptors and thus enhances norepinephrine release, while blockade of heteroreceptors on serotonergic neurons increases serotonin release. With 5-HT2 and 5-HT3 receptor blockade, enhanced serotonin release results in a net increase in 5-HT1 mediated neurotransmission (de Boer 1995), which is considered to be related to the antidepressant effect of mirtazapine (de Boer 1996).

Mirtazapine is usually prescribed to patients at 15 mg/day as the starting dose and the maintenance dose is generally not more than 45 mg/day. Because of the unique pharmacology of mirtazapine, antihistaminergic effects have been thought to predominate at lower doses (causing drowsiness, sedation), whilst noradrenergic neurotransmission increases with increasing doses to counteract some of the antihistaminergic effects. Dry mouth, sedation, and increases in appetite and body weight have been reported as the most common adverse effects (Anttila 2001).

Why it is important to do this review

The efficacy of mirtazapine has been investigated through several meta-analyses, especially compared with a placebo or amitriptyline. A meta-analysis of eight randomised controlled clinical trials (RCTs) showed that mirtazapine is superior to placebo and is comparable to amitriptyline for the treatment of patients with major depression (Fawcett 1998). However, that review is outdated because 11 years have elapsed since its publication.

Regarding a comparison with SSRIs, only limited evidence has been established to date. A Cochrane review for fluoxetine showed that mirtazapine was more effective than fluoxetine (Cipriani 2005). Several RCTs have examined the efficacy of mirtazapine in comparison with other newer antidepressants, including paroxetine (Benkert 2000; Schatzberg 2002), sertraline (Behnke 2003), citalopram (Leinonen 1999) and trazodone (van Moffaert 1995). In those RCTs, mirtazapine was consistently reported to have a faster onset of action than the other agents on core symptoms of depression (Thase 2005; Thase 2006) but, to our knowledge, no overall systematic quantitative review has been published for these comparisons.

In addition, the profile of adverse events related to mirtazapine has been controversial. Mirtazapine was thought to have no association with sexual side effects (Anttila 2001; Kent 2000). However, a cross-sectional survey has shown that 41% of patients taking mirtazapine in primary care clinics experienced sexual dysfunction, similar to paroxetine (Clayton 2002). Therefore, the comparative efficacy and adverse effects of mirtazapine against antidepressants other than fluoxetine remain uncertain.

A group of researchers agreed to join forces under the rubric of the Multiple Meta-Analysis of New Generation Antidepressants Study (MANGA study) to systematically review all available evidence for each specific, newer antidepressant. We have, to date, completed or planned head-to-head meta-analyses for individual newer antidepressants in comparison with all the other antidepressive agents. The newer antidepressants included bupropion, citalopram (Imperadore 2007), duloxetine (Nose 2007), escitalopram (Cipriani 2009b),

fluoxetine (Cipriani 2005), fluvoxamine (Omori 2010), milnacipran (Nakagawa 2009), paroxetine (Cipriani 2007a), sertraline (Cipriani 2009), venlafaxine (Cipriani 2007b), reboxetine (Churchill 2009) and mirtazapine.

Although the overall efficacy, tolerability and information about the adverse event profile of mirtazapine in treatment for major depression, in comparison with other antidepressants, has been published elsewhere (Watanabe 2008; Watanabe 2010) the presented data have been outdated.

This review aims to provide a comprehensive summary of the information about the overall efficacy, tolerability and adverse events for mirtazapine compared with other antidepressants used in the treatment of major depression, and will update previously published findings (Watanabe 2008; Watanabe 2010).

OBJECTIVES

1. To determine the efficacy of mirtazapine in comparison with other antidepressive agents in acute-phase treatment for major depression
2. To review the acceptability of mirtazapine in comparison with that of other antidepressive agents in acute-phase treatment for major depression
3. To investigate the adverse effects of mirtazapine in comparison with other antidepressive agents in acute-phase treatment for major depression

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials, with individual participant or cluster randomisation, were included. Quasi-randomised trials, such as those allocating participants by using alternate days of the week, were excluded. For trials which had a crossover design only results from the first randomisation period were considered.

Types of participants

Inclusion criteria: participants aged 18 years or older, of both sexes and with a primary diagnosis of unipolar major depression diagnosed according to any of the standardised criteria: Feighner criteria, Research Diagnostic Criteria, DSM-III (APA 1980), DSM-III-R (APA 1987), DSM-IV (APA 1994) or ICD-10 (WHO 1992) were included. We included the following subtypes: chronic, with catatonic features, with melancholic features, with atypical features, postpartum onset, seasonal pattern. participants with co-morbid mental disorders that were not their primary diagnosis were included. Studies in which less than 20% of the participants suffered from bipolar depression were included.

Exclusion criteria: A concurrent primary diagnosis of Axis I or II disorders was an exclusion criterion. We excluded participants with the subtype: with psychotic features. Participants with a serious concomitant medical illness were also excluded.

Types of interventions

Experimental intervention: The experimental intervention was mirtazapine used for acutephase treatment of major depression. No restrictions on dose, frequency, intensity or duration of treatment were applied.

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

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

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

Trials in which mirtazapine was compared to another type of psychopharmacological agent (e.g. anxiolytics, anti-convulsants, antipsychotics or mood-stabilisers) were excluded. Trials in which mirtazapine or the comparator agent was used as an augmentation strategy were also excluded.

Types of outcome measures—We decided, a priori, to subdivide the treatment outcome indices into:

1. at two weeks after commencement of treatment;
2. after the conclusion of the acute-phase treatment (between 6 and 12 weeks)
3. after the conclusion of continuation treatment (between 4 and 6 months).

After the conclusion of the acute-phase treatment was defined as the primary time point. For each outcome, a risk ratio (RR) of mirtazapine in comparison with each type of antidepressant class was examined in the primary analyses (see Data synthesis).

Primary outcomes

Response: The primary outcome in our systematic review was defined as a response, after the conclusion of acute-phase treatment, represented by a reduction of at least 50% in the score on the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery 1979), or ‘much or very much improved’ (score 1 or 2) on the CGI-Improvement measure (Guy 1970). We did not employ the original authors’ definitions of the primary outcomes per se because investigators or journal editors might selectively withhold some of the measured outcomes because of the poor strength of the result (outcome reporting bias) (Furukawa 2007). Among the three response criteria, we used the HAM-D for the primary outcome whenever possible, even when we needed to impute response rates (see Data synthesis) because the HAM-D has

been the gold standard measure of depression severity for clinical trials of antidepressants (Williams 2001).

Secondary outcomes

Efficacy outcomes

Remission: We used remission as the secondary outcome, represented by a score of 7 or less on the 17-item HAM-D, of 8 or less in all the other longer versions of HAM-D, and of 11 or less on the MADRS.

Depression severity: Group mean scores at the end of the trial on the HAM-D, or MADRS, or any other depression scale. We applied a looser form of ITT analyses, whereby all the participants with at least one post-baseline measurement were represented by their last observations carried forward.

Social adjustment: Social adjustment, social functioning including the Global Assessment of Function (Luborsky 1962) scores.

Health-related quality of life (HRQoL): The HRQoL outcomes were included in the analysis when they were reported in a validated scale such as SF-12 or SF-36 (Ware 1993), HoNOS (Wing 1994) and WHO-QOL (WHOQOL Group 1998).

With regard to continuous outcomes, when data were provided in a trial both as endpoint scores and as change scores, change scores were included in the analysis because change scores were preferable in meta-analyses (Norman 1989; Wiebe 2003).

Tolerability and acceptability outcomes

1. Number of participants who dropped out during the trial due to any reason.
2. Number of participants who dropped out during the trial due to the development of adverse event.
3. Total number of participants experiencing at least some adverse events during the trial.
4. Number of participants experiencing the following specific individual adverse events: hypertension or tachycardia; hypotension or bradycardia; sweating; constipation; diarrhoea; dry mouth or decreased salivation; nausea, vomiting or gastric distress; weight gain or increased appetite; weight loss or anorexia; sexual dysfunction; anxiety or agitation; dizziness, vertigo, faintness; fatigue, tiredness, asthenia; headache; tremor; sleep disturbance; sleepiness, drowsiness, somnolence; completed suicide, and suicide attempt.

To avoid missing any relatively rare or unexpected side effects in the data extraction phase, we collected all adverse events data reported in the literature and discussed ways to summarise them post hoc. Descriptive data regarding adverse event profiles were extracted from all available studies. Only studies reporting the number of participants experiencing individual adverse events were retained. Due to the variety in reporting of adverse events as

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presented from the study authors' descriptions, terms describing similar adverse events were combined.

Search methods for identification of studies

The Cochrane, Depression, Anxiety and Neurosis Review Group's Specialised Register (CCDANCTR)—CCDAN maintain two clinical trials registers at their editorial base in Bristol, UK, a references register and a studies based register. The CCDANCTR-References Register contains over 27,500 reports of trials in depression, anxiety and neurosis. Approximately 60% of these reports have been tagged to individual trials. Coded trial records are held in the CCDANCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Reports of trials for inclusion in the Group's registers are collated from routine (weekly), generic searches of MEDLINE (1950-date), EMBASE (1980 - date) and PsycINFO (1967 - date); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials are also sourced from international trials registers c/o the World Health Organisation's trials portal (ICTRP), drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCDAN's generic search strategies used to identify RCTs can be found on the CCDAN website.

Electronic searches—The CCDANCTR-Studies Register was searched using the following terms:

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

And

INTERVENTION = Mirtazapine

The CCDANCTR-References Register was searched using free-text terms to identify any additional untagged references: ((Depress* or Dysthymi* or "Adjustment Disorder*" or "Mood Disorder*" or "Affective Disorder" or "Affective Symptoms") and Mirtazapine)

Both registers were searched up to July 2011.

Searching other resources—Trial databases and trial results registers were searched for additional unpublished or ongoing studies. These included: the World Health Organisation's trials portal (ICTRP); ClinicalTrials.gov and ClinicalStudyResults.org. The FDA database drugs@fda.gov was also searched in June 2010.

Personal communication: Experts in the field were asked if they knew of any study which met the inclusion criteria for this review. The pharmaceutical company Organon who market (and developed) Mirtazapine was also contacted and asked to provide unpublished data (December 8, 2006).

Reference checking: The reference lists of reports of all included studies, previous systematic reviews and major textbooks of affective disorder, written in English, were checked for published reports and citations of unpublished research. A citation search was conducted to identify articles citing any of the included studies.

Data collection and analysis

Selection of studies—Studies relating to mirtazapine were identified by the electronic search of CCDANCTR-Studies and CCDANCTR-References and other complementary searches by the Trials Search Coordinator of CCDAN. They were scanned by one author (NW) as over-inconclusively as possible, firstly based on the title and abstracts. Those studies which met the following inclusion criteria constituted the preliminary list and their full texts were retrieved.

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

All the full text articles were then assessed independently by two review authors (NW and IMO) to see if they meet the strict inclusion criteria. When the raters disagreed the final rating was made by consensus, with the involvement of another author (TAF). Considerable care was taken to exclude duplicate publications.

Data extraction and management—Two authors (NW and IMO) independently extracted data from the included studies concerning participant characteristics (age, sex, depression diagnosis, comorbidity, depression severity, antide-pressant treatment history for the index episode, study setting), intervention details (intended dosage range, mean daily dosage actually prescribed, co-intervention if any, mirtazapine as investigational drug or as comparator drug, sponsorship) and outcome measures of interest. When any discrepancies between the data extracted by each author occurred, the final decision was made by consensus through discussion between the authors.

When the trial was a three (or more) armed trial that involved a placebo arm, the data were extracted from the placebo arm as well. Data were entered by a review author (NW) with double data entry to avoid input errors.

Assessment of risk of bias in included studies—The methodological quality of the selected trials was assessed by using criteria based on the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Each potential risk of bias was assessed by two review authors (NW, TAF) independently. All the judgements were made as low risk of bias, high risk of bias or unclear risk of bias (when insufficient information provided to permit judgement) and described for each trial in a ‘Methodological quality summary’ table (Figure 1).

Sequence generation: The method used to generate the allocation sequence was assessed to ascertain whether the sequence was adequately generated. Judgements were made as low risk of bias when the investigators described a random component in the sequence

generation process, such as referring to a random number table, using a computerised random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots and minimization.

Allocation concealment: Quality of allocation concealment in the randomisation to treatment conditions was assessed to ascertain whether allocation was adequately concealed. The judgements were made as low risk of bias when participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; and sequentially numbered, opaque sealed envelopes.

Blinding: Quality of blinding was rated to ascertain whether the outcome measures were assessed by an independent assessor who was blind to treatment allocation. A self-report questionnaire can be a 'blind' measurement if the participants were adequately blinded to their allocated treatment. The judgements were made as low risk of bias when any one of the following was done: no blinding, but the review authors judged that the outcome and the outcome measurement were not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

Incomplete outcome data: Adequate addressing of incomplete outcome data was regarded as low risk of bias both when less than 20% of the allocated participants to each group were assessed and results of the assessment were reported at the primary time point of the present review in both intervention groups regardless of the number of participants who dropped out from the allocated intervention, and when reasons for missing outcome data were unlikely to be related to the true outcome.

Selective outcome reporting: The completeness of outcome data was assessed to ascertain whether the primary outcome 'response' was adequately provided in the original report and no imputing (see Dealing with missing data) was required for our analysis at the primary time point, which was the end of acute-phase treatment.

Other sources of bias: Sponsorship bias was regarded as high risk of bias when the original study was funded by a pharmaceutical company or when other sources of potential bias were detected. Other sources of bias referred to any bias in certain circumstances, for example, in relation to trial design or setting.

Measures of treatment effect—See also Data synthesis.

Dichotomous data—Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated.

Continuous data—Mean differences or standardised mean differences (SMDs) and their 95% CIs were calculated (See Data synthesis).

Unit of analysis issues

Cluster-randomised trials: The effect size in cluster-randomised trials was estimated using the intracluster correlation coefficient (ICC), where provided, to adjust for cluster effects.

Crossover trials: It was planned to use the first active treatment phase in analyses.

Multi-intervention trials: For studies with two active or control arms, the results of both comparisons were pooled by dividing the opposite arm into two equal numbers for the purpose of avoiding unit of analysis errors (Ramsay 2005).

Dealing with missing data

Dichotomous data: The analysis was calculated on an intention-to-treat (ITT) basis, where dropouts were always included in the analysis. Where participants withdrew from the trial before the endpoint, it was assumed that they had not experienced the outcome by the end of the trial.

When the efficacy dichotomous outcomes of interest were not reported but baseline and endpoint means and standard deviations (SD) of the HAM-D (or any other depression scale) were provided, we imputed the number of participants with responses and remission by using a validated statistical method, for example according to the following formula for the response outcome (Furukawa 2005):

number of responders at endpoint = number of participants at endpoint * normal standard distribution corresponding to (50% of the baseline score - endpoint score)/SD.

When the SD was not reported, its value was imputed by pooling the SDs reported in the other included trials (Altman 1996; Furukawa 2006), although using both of these imputing methods at the same time has not yet been empirically supported.

Continuous data: 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.

Only data reported with a point estimate, SDs and number of participants at the time point were included in the analysis. The above imputation method for SDs was not used because we could not assess the skewness of the data without SDs (See Data synthesis).

Assessment of heterogeneity—Heterogeneity between the studies was assessed by using the Chi^2 test, the I^2 statistic and by visual inspection of the results. A P value of less than 0.1 for the Chi^2 test or an I^2 value of greater than 50% were considered to be suggestive of heterogeneity, although these definitions as recommended in the Cochrane Handbook might be arbitrary because they depends on the number of studies included in the analysis, the direction and magnitude of the treatment effects and the strength of evidence against the null hypothesis of homogeneity. Where significant heterogeneity was detected and was unexplained by subgroup analysis, other potential sources of the heterogeneity were investigated.

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

Data synthesis—All the analyses were conducted by NW using RevMan 5.0.

A random-effects model was used to pool the results of single studies because we anticipated this model was likely to provide the best fit to the data given the heterogeneity (Furukawa 2002). In addition, the model is more conservative than a fixed-effect model and incorporates both within-study and between-study variance.

Dichotomous data: A random-effects model using the odds ratio (OR) was used for the primary analysis rather than a random-effects model using risk ratio (RR) because it has been shown to have the highest generalisability in our empirical examination of summary effect measures for meta-analyses (Furukawa 2002). The 95% confidence interval (CI) was presented along with its precise P value. The robustness of this summary measure was routinely examined by checking the fixed-effect model using ORs, and the random-effects model using RRs. 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.

Continuous data: Continuous data were analysed using mean differences or standardised mean differences (where different measurement scales were used) and the random-effects model. The 95% CI was presented along with its precise P value. Skewed data were presented descriptively and were not included in the meta-analyses. Outcomes were considered skewed when the mean was smaller than twice the SD.

P values and statistical significance: We did not set any alpha level for ‘statistical significance’ in the outcomes. Instead, the effect estimate, its 95% CI and the precise P value were always presented because the conventional significance threshold at P value of 0.05 is an arbitrary one, as P values are smaller in a larger study than in a smaller study (Higgins 2008).

Subgroup analysis and investigation of heterogeneity—Subgroup analyses should be performed and interpreted with caution because multiple analyses could lead to false positive conclusions (Oxman 1992). We planned to perform the following subgroup analyses for the primary outcome.

1. For individual comparator drugs.
2. For the treatment settings (e.g. psychiatric inpatients or outpatients in primary care), because the treatment setting is thought to reflect the severity of depression.
3. Elderly participants (aged 65 years or older) separately from other adult participants.

The subgroup analyses have been amended from the published protocol, in which there are five subgroup analyses (Mirtazapine dosing, Comparator dosing, Depression severity,

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Treatment settings, Elderly participants), because adequate numbers of studies were not available for these analyses.

Where significant heterogeneity was unexplained by subgroup analysis other potential sources, such as depression severity at baseline, focusing on refractory depression and inclusion of bipolar participants, were investigated.

Sensitivity analysis—Sensitivity analyses were also planned. By limiting the studies to those with higher quality we examined if the results changed and we meant to check for the robustness of the observed findings for the primary outcome by:

1. excluding trials for which the response rate at the end of the acute-phase treatment had to be calculated based on the above imputation method;
2. excluding trials funded by or with at least one author affiliated to a pharmaceutical company marketing mirtazapine. This latter sensitivity analysis is 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 have been increasing over the last 20 years (Buchkowsky 2004).

The sensitivity analyses have been amended from the published protocol, in which there are six sensitivity analyses (excluding trials with unclear concealment of random allocation and/or unclear double blinding, excluding trials whose drop out rate is greater than 20%, performing the worst case/best case scenario ITT, excluding trials for which the response rates had to be calculated based on the imputation method/borrowed from other trials, examination of “wish bias” by comparing mirtazapine as investigational drug vs mirtazapine as comparator, excluding studies funded by the pharmaceutical company marketing mirtazapine), because adequate numbers of studies were not available for these analyses.

RESULTS

Description of studies

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

Results of the search—Our initial search strategy yielded 94 trials including 135 references (Figure 2). After examining their titles and abstracts, 82 trials appeared to meet the inclusion criteria and their full texts were obtained. Among these, 45 studies were written in Chinese. We commissioned a professional translator for the full translation of these papers. The translation process is still ongoing, so in the present review we considered all Chinese studies as awaiting assessment. Through a contact with authors of the trials, experts in the area and the manufacturer of mirtazapine, we also obtained information on unpublished data not yet available in the published information (Hoyberg 1996; Schoemaker 2002; Thase 2000) and unpublished data from the manufacturer (Organon 85146). Eight studies were finally excluded. Twenty-nine studies with a total enrolment of 4974

participants were identified as satisfying our inclusion criteria and were included in our final analyses.

Included studies—See: Characteristics of included studies.

Design—All the included trials employed randomisation for individual participants. Neither cluster nor crossover trials were identified. The participants were followed up for six weeks (range: 2 to 24 weeks) in a majority of the trials (15 trials). Only one trial reported data after the end of the continuation treatment (at 24 weeks) (Wade 2003).

Setting—Seven trials enrolled psychiatric inpatients only (Brunnauer 2008; Guelfi 2000; Organon 85146; Richou 1995; Schule 2006; van Moffaert 1995; Zivkov 1995), the focus was placed on participants in primary care in one study (Wade 2003) and both psychiatric inpatients and outpatients were included in the other trials.

Participants—In all but one trial (Marttila 1995) the participants were diagnosed to have depression based on the DSM. Elderly participants (over 65 years of age) were included in 16 trials, two trials focused only on older adults or elderly participants. One trial limited the participants to those aged 60 years or older (Hoyberg 1996) and the other limited participants to those aged 65 years or older (Schatzberg 2002). The participants with psychiatric or physical disorders as co-morbidities with depression were excluded in a great majority of the trials (25 trials). Female participants who were potentially or actually pregnant or breastfeeding on entry into the trials were also excluded in 20 trials and the other trials did not state whether such participants were included or excluded. Two trials focused on refractory or treatment-resistant depression (Fava 2006; Thase 2000).

Interventions—All but four trials (Amini 2005; Benkert 2006; Schule 2006; Winokur 2003) employed flexible dosing regimens for both the mirtazapine and comparator arms. No trials examined different doses or schedules of the same therapy.

In terms of the comparator drug, in ten trials a TCA (amitriptyline in seven; clomipramine, doxepin and nortriptyline each in one) was used as the comparator drug; in 13 trials an SSRI (citalopram in one, fluoxetine in five, fluvoxamine in one, paroxetine in four and sertraline in two) was used; in two an SNRI (venlafaxine) was used; in two an heterocyclic AD (trazodone) was used; and in two a newer AD (reboxetine) was used. No trials using any other SNRIs as the comparator, such as duloxetine or milnacipran, were identified.

A placebo pill was used as a comparator intervention in three trials (Bremner 1995; Halikas 1995; Smith 1990).

Outcomes—In all but two trials (Fava 2006; Leinonen 1999) the 17- or 21-item HAM-D was used for reporting the response. With regard to the acceptability outcomes, 23 trials provided the number of dropouts due to any reason and 23 trials reported the number of dropouts due to the development of adverse event during the trials; these trial results did not always overlap.

Excluded studies—See: Characteristics of excluded studies. Eight studies were excluded for the following reasons: not a relevant diagnostic status (Kremer 1995; Peyron 1996; Tulen 1996), a review of other studies (Bruijin 1996; Kasper 1997a; Kasper 1997b), not employing random allocation (Zourkova 2001), and combined therapy of mirtazapine and another antidepressant (Blier 2004).

Ongoing studies—No ongoing studies were identified.

Studies awaiting classification—Forty-six studies written in Chinese are awaiting classification. One study (Catterson 1996a) needs further data for checking if the study meets the strict eligibility criteria. Seven studies (Blier 2009; Fang 2010; Kang 2009; Kim 2011; Paslakis 2010; Sarginson 2010; Scharnholz 2010) identified after the completion of the review are classified in this category.

Risk of bias in included studies

Two of the three review authors (NW, IMO, TAF) independently assessed study quality. Any discrepancy between two authors was dissolved upon discussion (see: Figure 1; Figure 3).

Sequence generation—None of the trials described the sequence generation process.

Allocation—None of the trials reported whether allocation concealment was adequately performed.

Blinding—All trials but one (Fava 2006) were undertaken on a double-blind basis, but none of the trials reported information to judge whether it was likely or unlikely that the blinding had been broken.

Incomplete outcome data—Only three trials (Amini 2005; Bremner 1995; Leinonen 1999) were rated as adequate in terms of addressing incomplete outcome data.

Selective reporting—Outcomes in terms of the primary outcome (response) at the primary time point (at the end of acute-phase treatment) were obtained in all but two trials (Hoyberg 1996; Winokur 2003) without using the imputation method.

Other potential sources of bias—One study (Fava 2006) was funded by the National Institute of Mental Health (NIMH), and one study (Amini 2005) was unclear in terms of sponsorship bias. The other studies were sponsored by, or had at least one author affiliated to, a pharmaceutical company.

No other potential sources of bias were identified.

Effects of interventions

ORs for the efficacy data that were larger than one (falling to the right of the midline in a graph) and those for the acceptability and tolerability data that were smaller than one indicate a difference in favour of mirtazapine.

1. Mirtazapine versus tricyclic antidepressants (TCAs)

Primary analysis

1.1 Primary outcome: response: There was no robust evidence to detect a difference between mirtazapine and TCAs in terms of the response outcome at two weeks (8 studies; OR 0.85, 95% CI 0.64 to 1.13, P = 0.27) (Analysis 1.1; Figure 4) and at end of the acute-phase treatment (9 studies; OR 0.89, 95% CI 0.72 to 1.10, P = 0.29) (Analysis 1.2; Figure 5). No substantial heterogeneity was observed.

1.2 Secondary outcomes

1.2.1 Remission: There was robust evidence to detect any difference between mirtazapine and TCAs in terms of the remission outcome at two weeks (8 studies; OR 0.85, 95% CI 0.55 to 1.32, P = 0.47) (Analysis 1.3) and at end of the acute-phase treatment (9 studies; OR 0.86, 95% CI 0.69 to 1.08, P = 0.19) (Analysis 1.4).

1.2.2 Depression severity: Two studies (Mullin 1996; Zivkov 1995) contributed to the meta-analysis at two weeks and one study (Organon 85146) did so at the end of acute-phase treatment. Information from studies with skewed data were not included in the meta-analysis but were included in a descriptive table (Analysis 1.32; Analysis 1.33). From the results of the meta-analysis, there was no robust evidence to detect a difference between mirtazapine and TCAs in terms of depression severity on a continuous scale at two weeks (2 studies; Analysis 1.5) and at the end of the acute-phase treatment (1 study; Analysis 1.6).

1.2.3 Social adjustment: One study (Mullin 1996) contributed to the meta-analysis at two weeks and three studies (Marttila 1995; Mullin 1996; Richou 1995) did so at the end of the acute-phase treatment. There was no robust evidence to detect a difference between mirtazapine and TCAs in terms of social adjustment at two weeks (1 study; Analysis 1.7) and at end of the acute-phase treatment (3 studies; Analysis 1.8).

1.2.4 Health-related quality of life (HRQoL): No data were available.

1.2.5 Withdrawal due to any reason: There was no robust evidence to detect a difference between mirtazapine and TCAs in terms of withdrawal due to any reason during the acute-phase treatment (7 studies; Analysis 1.9).

1.2.6 Withdrawal due to the development of an adverse event: There was no robust evidence to detect a difference between mirtazapine and TCAs in terms of withdrawal due to the development of an adverse event during the acute-phase treatment (8 studies; Analysis 1.10).

1.2.7 Having some adverse events: There was no robust evidence to detect a difference between mirtazapine and TCAs in terms of developing adverse events during the acute-phase treatment (2 studies; Analysis 1.11).

1.2.8 Individual adverse events: No data were available with regard to diarrhoea, weight loss and completed suicide. Mirtazapine was less likely than TCAs to bring on hypertension or tachycardia (4 studies; OR 0.44, 95% CI 0.24 to 0.81, P = 0.008) (Analysis 1.12) and

tremor (7 studies; OR 0.36, 95% CI 0.22 to 0.57, P < 0.0001) (Analysis 1.24). There was no robust evidence to detect a difference between mirtazapine and TCAs in terms of developing other types of individual adverse events.

Secondary analysis

1.3 Subgroup analysis and investigation of heterogeneity

1.3.1 Individual comparator drugs: There was no robust evidence to detect a difference between mirtazapine and any specific type of TCA comparator in terms of the response outcome during the acute-phase treatment (8 studies at 2 weeks: Analysis 1.1, 9 studies at end of acute-phase treatment:Analysis 1.2).

1.3.2 Treatment settings: No studies focused on participants in primary care clinics only. Limiting findings to studies focusing on psychiatric inpatients, there was no robust evidence to detect a difference between mirtazapine and TCAs in terms of the response to acute-phase treatment (2 studies at 2 weeks: Analysis 1.28, 3 studies at end of the acute-phase treatment: Analysis 1.29).

1.3.3 Elderly participants: No studies focused on elderly participants only.

1.4 Sensitivity analysis

1.4.1 Studies without imputation: All but one study (Hoyberg 1996) did not need any imputation method for the primary outcome at the end of the acute-phase treatment. Limiting findings to these studies, there was no robust evidence to detect a difference between mirtazapine and TCAs in terms of the response to acute-phase treatment (7 studies at 2 weeks: Analysis 1.30, 8 studies at end of the acute-phase treatment:Analysis 1.31).

1.4.2 Studies without sponsorship bias: From one study (Fava 2006), there was no robust evidence to detect a difference between mirtazapine and TCAs in the response to acute-phase treatment.

2. Mirtazapine versus selective serotonin reuptake inhibitors (SSRIs)

Primary analysis

2.1 Primary outcome: response: In comparison with SSRIs, mirtazapine was shown to be significantly more effective in terms of response at two weeks (12 studies; OR 1.57, 95% CI 1.30 to 1.88, P < 0.00001) (Analysis 2.1; Figure 6) and at the end of acute-phase treatment (12 studies; OR 1.19, 95% CI 1.01 to 1.39, P = 0.04) (Analysis 2.2; Figure 7). There was no robust evidence to detect a difference between mirtazapine and SSRIs at the end of the continuation treatment (at 24 weeks) based on one study (Wade 2003) (1 study; OR 1.60, 95% CI 0.91 to 2.81, P = 0.10) (Analysis 2.3). No substantial heterogeneity was observed at any of the three time points.

2.2 Secondary outcomes

2.2.1 Remission: Mirtazapine was shown to be significantly more effective than SSRIs in terms of the remission outcome at two weeks (12 studies; OR 1.82, 95% CI 1.36 to 2.44, P < 0.0001) (Analysis 2.4). At the end of the acute-phase treatment, there was no robust

evidence to detect a difference between mirtazapine and SSRIs (12 studies; OR 1.17, 95% CI 0.98 to 1.40, P = 0.08) (Analysis 2.5). There was no robust evidence to detect a difference between mirtazapine and SSRIs at the end of the continuation treatment (1 study; OR 1.89, 95% CI 1.01 to 3.54, P = 0.05) (Analysis 2.6).

2.2.2 Depression severity: No data were available for the meta-analysis. Information from studies with skewed data were not included in the meta-analysis but in a descriptive table (2 studies at 2 weeks: Analysis 2.31, 3 studies at end of the acute-phase treatment: Analysis 2.32).

2.2.3 Social adjustment: No data were available.

2.2.4 Health-related quality of life (HRQoL): No data were available.

2.2.5 Withdrawal due to any reason: There was no robust evidence to detect a difference between mirtazapine and SSRIs in terms of withdrawal due to any reason during the acute-phase treatment (11 studies; Analysis 2.7).

2.2.6 Withdrawal due to the development of an adverse event: There was no robust evidence to detect a difference between mirtazapine and SSRIs in terms of withdrawal due to the development of an adverse event during the acute-phase treatment (11 studies; Analysis 2.8).

2.2.7 Having some adverse events: There was no robust evidence to detect a difference between mirtazapine and SSRIs in terms of developing any adverse events during the acute-phase treatment (7 studies; Analysis 2.9).

2.2.8 Individual adverse events: No data were available with regard to hypertension or tachycardia and completed suicide. In comparison with SSRIs, mirtazapine was more likely to cause dry mouth (10 studies; OR 1.80, 95% CI 1.37 to 2.36, P < 0.0001) (Analysis 2.14), weight gain or increased appetite (11 studies; OR 4.23, 95% CI 2.93 to 6.11, P < 0.00001) (Analysis 2.16), fatigue (8 studies; OR 1.53, 95% CI 1.08 to 2.15, P = 0.02) (Analysis 2.21) and somnolence (11 studies; OR 1.81, 95% CI 1.39 to 2.37, P < 0.0001) (Analysis 2.25) but less likely to cause sweating (5 studies; OR 0.25, 95% CI 0.15 to 0.44, P < 0.00001) (Analysis 2.11), diarrhoea (8 studies; OR 0.57, 95% CI 0.41 to 0.80, P = 0.001) (Analysis 2.13), nausea or vomiting (11 studies; OR 0.33, 95% CI 0.26 to 0.43, P < 0.00001) (Analysis 2.15), sexual dysfunction (4 studies; OR 0.31, 95% CI 0.13 to 0.74, P = 0.009) (Analysis 2.18), headache (11 studies; OR 0.69, 95% CI 0.56 to 0.86, P = 0.0008) (Analysis 2.22), tremor (5 studies; OR 0.34, 95% CI 0.18 to 0.66, P = 0.001) (Analysis 2.23) or sleep disturbance (5 studies; OR 0.52, 95% CI 0.31 to 0.86, P = 0.01) (Analysis 2.24). There was no robust evidence to detect a difference between mirtazapine and SSRIs in terms of developing other types of individual adverse events.

Secondary analysis

2.3 Subgroup analysis and investigation of heterogeneity

2.3.1 Individual comparator drugs: In terms of response at two weeks, mirtazapine was shown to be significantly more effective than paroxetine (3 studies; OR 2.39, 95% CI 1.42 to 4.02, P = 0.001) and sertraline (2 studies; OR 1.45, 95% CI 1.04 to 2.02, P = 0.03) (Analysis 2.1). Mirtazapine was shown to be significantly more effective than fluoxetine at the end of the acute-phase treatment (5 studies; OR 1.55, 95% CI 1.07 to 2.23, P = 0.02) (Analysis 2.2). There was no robust evidence to detect a difference between mirtazapine and the other individual comparator drugs.

2.3.2 Treatment settings: No studies focused on psychiatric inpatients or participants in primary care clinics only.

2.3.3 Elderly participants: Based on one study (Schatzberg 2002), mirtazapine was shown to be significantly more effective than paroxetine at two weeks (OR 2.59, 95% CI 1.35 to 4.97, P = 0.004) (Analysis 2.1). There was no robust evidence to detect a difference between mirtazapine and paroxetine at the end of the acute-phase treatment (OR 1.41, 95% CI 0.86 to 2.32, P = 0.17) (Analysis 2.2).

2.4 Sensitivity analysis

2.4.1 Studies without imputation: All but one study (Winokur 2003) did not need any imputation method for the primary outcome at the end of the acutephase treatment. Limiting findings to these studies, mirtazapine was shown to be significantly more effective than SSRIs in terms of response at two weeks (11 studies; OR 1.58, 95% CI 1.31 to 1.90, P < 0.00001) (Analysis 2.29). There was no robust evidence to detect a difference between mirtazapine and SSRIs at the end of the acute-phase treatment (11 studies; OR 1.17, 95% CI 1.00 to 1.38, P = 0.05) (Analysis 2.30).

2.4.2 Studies without sponsorship bias: All studies were funded by a pharmaceutical company.

3. Mirtazapine versus serotonin-noradrenaline reuptake inhibitors (SNRIs)

Primary analysis

3.1 Primary outcome: response: Mirtazapine was shown to be significantly more effective than venlafaxine at two weeks (2 studies; OR 2.29, 95% CI 1.45 to 3.59, P = 0.0003) (Analysis 3.1) and at the end of the acute-phase treatment (2 studies; OR 1.53, 95% CI 1.03 to 2.25, P = 0.03) (Analysis 3.2). No substantial heterogeneity was observed.

3.2 Secondary outcomes

3.2.1 Remission: Mirtazapine was shown to be significantly more effective than venlafaxine in terms of the remission outcome at two weeks (2 studies; OR 2.34, 95% CI 1.07 to 5.13, P = 0.03) (Analysis 3.3). At the end of the acute-phase treatment, there was no robust evidence to detect a difference between mirtazapine and venlafaxine (2 studies; OR 1.55, 95% CI 0.98 to 2.47, P = 0.06) (Analysis 3.4).

3.2.2 Depression severity: No data were available for the meta-analysis.

3.2.3 Social adjustment: No data were available.

3.2.4 Health-related quality of life (HRQoL): No data were available.

3.2.5 Withdrawal due to any reason: Mirtazapine was shown to be significantly more effective than venlafaxine in terms of withdrawal due to any reason (2 studies; OR 0.65, 95% CI 0.43 to 0.99, P = 0.04) during the acute-phase treatment (Analysis 3.5).

3.2.6 Withdrawal due to the development of adverse event: There was no robust evidence to detect a difference between mirtazapine and venlafaxine in terms of withdrawal due to the development of adverse event during the acute-phase treatment (2 studies; Analysis 3.6).

3.2.7 Having some adverse events: There was no robust evidence to detect a difference between mirtazapine and venlafaxine in terms of developing any adverse events during the acute-phase treatment (1 study; Analysis 3.7).

3.2.8 Individual adverse events: No data were available with regard to hypertension or tachycardia, diarrhoea, weight gain or increased appetite, weight loss or anorexia, sexual dysfunction, dizziness or vertigo, tremor and attempted suicide. In comparison with venlafaxine, mirtazapine was more likely to cause fatigue (1 study; OR 2.43, 95% CI 1.30 to 4.55, P = 0.006) (Analysis 3.14) but less likely to cause sweating (1 study; OR 0.03, 95% CI 0.00 to 0.45, P = 0.01) (Analysis 3.9), constipation (1 study; OR 0.22, 95% CI 0.06 to 0.83, P = 0.02) (Analysis 3.10) or sleep disturbance (1 study; OR 0.02, 95% CI 0.00 to 0.41, P = 0.01) (Analysis 3.16). There was no robust evidence to detect a difference between mirtazapine and venlafaxine in terms of developing other types of individual adverse events.

Secondary analysis

3.3 Subgroup analysis and investigation of heterogeneity

3.3.1 Individual comparator drugs: No studies focusing on SNRIs other than venlafaxine were identified.

3.3.2 Treatment settings: No studies focused on participants in primary care clinics only. In terms of inpatients, based on one study (Guelfi 2000) no robust evidence was observed to detect a difference between mirtazapine and venlafaxine at two weeks (OR 1.88, 95% CI 0.97 to 3.64, P = 0.06) (Analysis 3.1) or at the end of the acute-phase treatment (OR 1.64, 95% CI 0.87 to 3.10, P = 0.13) (Analysis 3.2).

3.3.3 Elderly participants: No studies focused on elderly participants only.

3.4 Sensitivity analysis

3.4.1 Studies without imputation: The two studies did not need any imputation method for the primary outcome at the end of the acute-phase treatment and the results of the analysis were the same as those from the primary analyses (Analysis 3.1; Analysis 3.2).

3.4.2 Studies without sponsorship bias: All studies were funded by a pharmaceutical company.

4. Mirtazapine versus heterocyclic antidepressants

Primary analysis

4.1 Primary outcome: response: There was no robust evidence to detect a difference between mirtazapine and an heterocyclic antidepressant (trazodone only) at two weeks (2 studies; OR 1.14, 95% CI 0.64 to 2.04, P = 0.66) (Analysis 4.1) or at the end of the acute-phase treatment (2 studies; OR 1.50, 95% CI 0.95 to 2.37, P = 0.08) (Analysis 4.2). No substantial heterogeneity was observed.

4.2 Secondary outcomes

4.2.1 Remission: There was no robust evidence to detect a difference between mirtazapine and trazodone at two weeks (2 studies; OR 1.00, 95% CI 0.36 to 2.80, P = 1.00) (Analysis 4.3) and at the end of the acute-phase treatment (2 studies; OR 1.38, 95% CI 0.76 to 2.52, P = 0.29) (Analysis 4.4).

4.2.2 Depression severity: No data were available for the meta-analysis.

4.2.3 Social adjustment: No data were available.

4.2.4 Health-related quality of life (HRQoL): No data were available.

4.2.5 Withdrawal due to any reason: There was no robust evidence to detect a difference between mirtazapine and trazodone in terms of withdrawal due to any reason during the acute-phase treatment (2 studies; OR 0.90, 95% CI 0.47 to 1.72, P = 0.76) (Analysis 4.5).

4.2.6 Withdrawal due to the development of an adverse event: There was no robust evidence to detect a difference between mirtazapine and trazodone in terms of withdrawal due to the development of an adverse event during the acute-phase treatment (2 studies; OR 0.61, 95% CI 0.25 to 1.51, P = 0.29) (Analysis 4.6).

4.2.7 Having some adverse events: No data were available.

4.2.8 Individual adverse events: No data were available with regard to sweating, diarrhoea, nausea, anxiety or agitation, fatigue, tremor and somnolence. In comparison with trazodone, mirtazapine was less likely to cause hypotension or bradycardia (OR 0.17, 95% CI 0.03 to 1.00, P = 0.05) (Analysis 4.8). There was no robust evidence to detect a difference between mirtazapine and trazodone in terms of developing other types of individual adverse events.

Secondary analysis

4.3 Subgroup analysis and investigation of heterogeneity

4.3.1 Individual comparator drugs: No studies focusing on antidepressants other than trazodone were identified.

4.3.2 Treatment settings: No studies focused on participants in primary care clinics only. In terms of inpatients, based on one study (van Moffaert 1995) no robust evidence was identified to detect a difference between mirtazapine and trazodone in terms of the response at two weeks (OR 1.16, 95% CI 0.54 to 2.48, P = 0.70) (Analysis 4.1) or at the end of the acute-phase treatment (OR 1.50, 95% CI 0.86 to 2.63, P = 0.16) (Analysis 4.2).

4.3.3 Elderly participants: No studies focused on elderly participants only.

4.4 Sensitivity analysis

4.4.1 Studies without imputation: The two studies did not need any imputation method for the primary outcome at the end of the acute-phase treatment and the results of the analysis were the same as those from the primary analysis (Analysis 4.1; Analysis 4.2).

4.4.2 Studies without sponsorship bias: All studies were funded by a pharmaceutical company.

5. Mirtazapine versus newer antidepressants

Primary analysis

5.1 Primary outcome: response: There was no robust evidence to detect a difference between mirtazapine and a newer antidepressant (reboxetine only) in terms of the response outcome at two weeks (1 study; OR 1.00, 95% CI 0.18 to 5.67, P = 1.00) (Analysis 5.1) and at end of the acute-phase treatment (1 study; OR 1.00, 95% CI 0.27 to 3.67, P = 1.00) (Analysis 5.2).

5.2 Secondary outcomes

5.2.1 Remission: There was no robust evidence to detect a difference between mirtazapine and reboxetine in terms of the remission outcome at two weeks (1 study; OR 1.00, 95% CI 0.06 to 17.18, P = 1.00) (Analysis 5.3) and at the end of the acute-phase treatment (1 study; OR 1.26, 95% CI 0.33 to 4.73, P = 0.74) (Analysis 5.4).

5.2.2 Depression severity: There was no robust evidence to detect a difference between mirtazapine and reboxetine in terms of the severity of depression at two weeks (1 study; SMD −0.37, 95% CI −1.00 to 0.25, P = 0.24) (Analysis 5.5). At the end of the acute-phase treatment the data were skewed and presented in a descriptive table (1 study; Analysis 5.8).

5.2.3 Social adjustment: No data were available.

5.2.4 Health-related quality of life (HRQoL): No data were available.

5.2.5 Withdrawal due to any reason: Not estimable because no participant in either group withdrew due to any reason (2 studies; Analysis 5.6).

5.2.6 Withdrawal due to the development of an adverse event: Not estimable, because no participant in either group withdrew due to the development of an adverse event (2 studies; Analysis 5.7).

5.2.7 Having some adverse events: No data were available.

5.2.8 Individual adverse events: No data were available with regard to any individual adverse event.

Secondary analysis

5.3 Subgroup analysis and investigation of heterogeneity

5.3.1 Individual comparator drugs: No studies focusing on antidepressants other than reboxetine were identified.

5.3.2 Treatment settings: The two studies focused on inpatients.

5.3.3 Elderly participants: No studies focused on elderly participants only.

5.4 Sensitivity analysis

5.4.1 Studies without imputation: One study needed the imputation method for the primary outcome at two weeks. The other provided no usable data for the primary outcome.

5.4.2 Studies without sponsorship bias: The two studies were funded by a pharmaceutical company.

6. Funnel plot analysis—There was no robust evidence of publication bias or other small study effects based on visual inspections of the funnel plot with regard to the primary outcome (response) at the primary time point (at the end of the acute-phase treatment) (Figure 8).

DISCUSSION

Summary of main results

This systematic review and meta-analysis examined the efficacy, acceptability and tolerability of mirtazapine for the acute-phase treatment for depression, in comparison with other antidepressive agents.

In terms of the primary outcome, overall a response was achieved at two weeks in 616 (26.6%) of the 2316 participants treated with mirtazapine, and in 1413 (61.0%) out of the 2316 participants treated with mirtazapine at the end of the acute-phase treatment. In terms of one of the secondary outcomes, a remission was achieved in 222 (9.6%) of the 2316 participants treated with mirtazapine at two weeks, and in 847 (36.6%) out of the 2316 participants treated with mirtazapine at the end of acute-phase treatment. In terms of acceptability, 512 (25.2%) out of the 2030 participants treated with mirtazapine withdrew from treatment at some time point during the course of treatment.

We concluded from the results that there was no robust evidence to detect a difference between mirtazapine and other types of antidepressants in terms of the response outcome at the end of the acute-phase treatment, at approximately six weeks. At two weeks, mirtazapine is likely to be more effective than either SSRIs or SNRIs, especially paroxetine and

venlafaxine. These results were confirmed even after an additional sensitivity analysis was conducted that excluded the two trials (Fava 2006; Thase 2000) that focused on treatment-resistant depression. In terms of tolerability, mirtazapine was not statistically significantly superior or inferior to other antidepressants.

Due to the unique pharmacological profile of mirtazapine, some anti-histaminergic effects have been thought to bring about drowsiness, sedation, dry mouth and an increase in appetite and body weight (Kent 2000). These side effects might result in a dropout of participants treated with mirtazapine. Approximately 70% of the participants treated with mirtazapine experienced at least one adverse event during the trials; and dry mouth, somnolence, weight or appetite increase, fatigue and headache were the most frequently observed. In comparison with SSRIs, treatment with mirtazapine was significantly more likely to lead to the development of dry mouth, weight gain or increased appetite, fatigue and somnolence but was significantly less likely to lead to the development of sweating, diarrhoea, nausea or vomiting, sexual dysfunction, headache, tremor and sleep disturbance.

Overall completeness and applicability of evidence

Participants—All but two studies (Fava 2006; Thase 2000) included in this review were not conducted for refractory depression. Psychiatric inpatients were included in five studies (Guelfi 2000; Organon 85146; Richou 1995; van Moffaert 1995; Zivkov 1995), participants in primary care were included in one study (Wade 2003) and the other 19 studies included both psychiatric inpatients and outpatients. The findings from this review, therefore, may not be representative of participants with refractory depression nor mildly affected participants frequently seen in primary care. Moreover, there was only one trial in which recruitment was wholly conducted for the depressive elderly (Schatzberg 2002. The findings from this review may therefore not be representative for the depressive elderly.

Interventions—Considering the often chronic and recurrence-prone presentation of major depression, long-term or follow-up interventions are often required for optimal treatment of this disorder. However, we could find only one study (Wade 2003) examining the long-term efficacy of mirtazapine for major depression.

Outcomes—Treatments for major depression should be assessed not only by psychiatric symptoms but also by general functioning and quality of life. However, no trials included in this review incorporated those outcomes. Considering that major depression is associated with a marked personal, social and economic morbidity, the under-investigation of these outcomes is a problem.

Quality of the evidence

No trials described methods of random sequence generation, and no trials reported the method of allocation concealment. It is conceivable that selection bias might have occurred in the trials included in this review. These methodologies should be adequately reported, as recommended in the CONSORT 2010 statement (Schulz 2010).

Physician and participant blinding were sought in all but one study (Fava 2006). However, no test of blinding success was conducted in any study. As a whole, there was little information on the outcome assessment process and the extent to which detection bias might have occurred was uncertain.

At the end of the acute-phase treatment, only four studies (Amini 2005; Bremner 1995; Brunnauer 2008; Leinonen 1999) reported the outcomes for an 80% or higher proportion of participants initially allocated to treatment conditions, and the other studies probably did not due to higher dropout rates. This high attrition rate could have influenced treatment outcomes.

All but two trials (Amini 2005; Fava 2006) included in our meta-analysis were funded or conducted under the advice of a manufacturer of mirtazapine. On the other hand, it has been repeatedly reported that industry sponsorship could influence trial outcomes in favour of a drug manufacturer (Als-Nielsen 2003; Lexchin 2003; Perlis 2005). The present review may suffer from sponsorship bias.

Potential biases in the review process

Some possible strengths and limitations of this review should be noted.

Strengths—First, we imputed the response and remission outcomes by applying the threshold of the most conventional and prevalent depression severity scales using a validated statistical method; we did not use the outcomes defined by the authors of the original trials. Although this methodology may appear arbitrary and to have possibly resulted in the loss of important information from the original trials, recent evidence has shown that in published RCTs the statistically significant outcomes for efficacy tend to be more fully reported than non-significant outcomes do, and that in 62% of trials at least one primary outcome was changed, introduced or omitted with reference to the protocols (Chan 2004; Furukawa 2007). For this reason, we decided to adhere to our criteria defined a priori for the response and remission outcomes and impute them if they were not unavailable from the original trials. We think that, as long as the selective reporting of outcomes remains prevalent, our methodology should be used in future systematic reviews.

Second, in addition to the response rate we took the remission rate into account as one of the outcomes. Previously reported metaanalyses have generally taken only the response outcome into account. However, a recent series of RCTs on the effectiveness of the sequential use of antidepressants and cognitive-behavioural therapy for depression, named STAR*D and one of which (Fava 2006) was included in our systematic review, revealed that the remission rate was more consistently associated with a better prognosis in terms of the long-term outcome than the response (Rush 2007). We, therefore, propose that all future studies on this subject should report on the remission outcome in addition to the response outcome for depression.

Limitations—First of all, industry sponsorship can influence trial outcomes in favour of a drug manufacturer. We were unable to rule out the possibility that the dosing of either mirtazapine or the comparator drug might have been designed in such a way as to induce

differences in favour of mirtazapine because the doses of the comparator drugs seemed lower than the usual doses in clinical practice in some of the included trials, especially in some of the trials comparing mirtazapine with fluoxetine or paroxetine (see: Characteristics of included studies). We initially intended to conduct a sensitivity analysis by excluding trials sponsored by pharmaceutical companies, but did not because only two out of the 25 trials were free of industry sponsorship.

The second limitation of the review was the treatment durations in the included RCTs (see also: Quality of the evidence). Sixteen out of the 25 included trials followed up the participants for only six weeks. The STAR*D study revealed that one third of those showing a response to treatment with antidepressants did so only after six weeks of therapy (and half of those who showed remission did so after six weeks) (Rush 2007). In addition, the durations of the RCTs included in our analysis were not sufficiently long to address the long-term side effects of mirtazapine. Long-term side effects should be considered as much as those observed in the short term because they could play a big part in determining the burden and effective outcome of therapies (Hoyberg 1996; Trivedi 2006); and rare but otherwise crucial outcomes could occur only in the long term. Furthermore, some adverse events including nausea tend to subside rapidly (Mullin 1996), whereas other adverse events including weight gain might be an ongoing problem that has potentially serious health implications in the long term. Future studies should include long-term adverse events among their outcomes. Addressing them may require a systematic review of studies dealing with the long-term effects of the drug in study designs other than RCTs; this review focused only on RCTs.

We are also concerned about the representativeness of the populations recruited in the included trials. Most of the included trials were carried out to investigate the efficacy of mirtazapine. Generally speaking, efficacy trials tend to include only symptomatic volunteers with no concomitant medical or psychiatric disease as opposed to enrolling participants seeking health care in typical clinical treatment settings (Trivedi 2006). Thus, efficacy trials may eventually lead to results with only limited ecological validity and generalisability to clinical practice. Future research on mirtazapine should include effectiveness trials enrolling participants seen in everyday practice.

Lastly, only one author was involved in the first stage of selecting studies and in making the preliminary list of potentially eligible studies, due to shortage of initial human resources in the review procedure. This might have led to possible human error in selection. However, selecting studies in this stage was conducted as over-inclusively as possible, and all the full text articles in this preliminary list were assessed by two review authors independently (NW and IMO). The final rating were made by consensus.

Agreements and disagreements with other studies or reviews

There have been several other reviews published recently that investigate the efficacy of mirtazapine in comparison with other types of antidepressants.

Although the faster onset of therapeutic action of mirtazapine in comparison with that of the SSRIs has been reported previously from a non head-to-head review of the results from

three RCTs (Quitkin 2001), our systematic review showed that this result on comparative efficacy was not the same for all SSRIs.

The most recent review compared the remission rates and time to remission in participants with major depression taking either mirtazapine or an SSRI through a meta-analysis of the individual participant data from 15 RCTs (Thase 2010). This review concluded that mirtazapine therapy resulted in significantly higher remission rates than SSRI therapy during six weeks of treatment, particularly within the first 15 days of treatment. Another recently published review compared the benefits and harms of 12 second-generation antidepressants for the treatment of depression in adults (Gartlehner 2008). It concluded that the clinical response and remission rates are similar among second-generation antidepressants, including mirtazapine, at the end of the acute-phase treatment. In terms of onset of action, this review concluded that mirtazapine has a significantly faster onset of action than citalopram, fluoxetine, paroxetine or sertraline.

The results from these reviews appear to be quite similar to those from the present review, although we have to be cautious to draw a definitive conclusion given the possibility of sponsorship bias and the width of confidence intervals of the outcomes.

We have recently published a multiple-treatments meta-analysis (MTM) in which our data for mirtazapine were merged with those for 11 other new generation antidepressants and both the direct and indirect comparisons were statistically pooled (Cipriani 2009a). The MTM offers a clinically meaningful synthesis when several competing treatments are available for one disease (Lu 2006; Lumley 2002; Salanti 2008), as is the case with major depression, while examining the overall strength and consistency of the network of evidence. In this MTM, mirtazapine emerged as one of the top four antidepressants in terms of response but not in terms of acceptability. The relative merits and drawbacks of direct versus MTM comparisons are still debatable (Bucher 1997; Ioannidis 2006; Song 2003) and we need to carefully weigh up and synthesise the direct with indirect comparisons.

AUTHORS' CONCLUSIONS

Implications for practice

Although mirtazapine is more likely to have a better efficacy profile than paroxetine or venlafaxine in terms of response at two weeks, in view of the similar efficacy of mirtazapine and other antidepressant agents at the end of the acute-phase treatment (at approximately six weeks), and of possible sponsorship bias, the results of the study led us to conclude that clinicians should also focus on other practically or clinically relevant considerations, such as differences in the side-effect profiles, to tailor the treatment to best fit an individual participant's needs.

Mirtazapine is less likely to cause tremor than TCAs, and nausea and sexual dysfunction than SSRIs, but is more likely to cause weight gain and somnolence.

Implications for research

Since the great majority of trials on the efficacy of mirtazapine are funded by the manufacturer, and thus might be subject to some sponsorship bias, future RCTs on the effectiveness of mirtazapine should be funded by non-profit organizations. Furthermore, future trials should include appropriate QoL outcome measures and should adequately report the method of generation of random sequence, allocation concealment, and blinding in accordance with the CONSORT 2010 statement. Finally, the effectiveness of mirtazapine should be investigated by conducting RCTs recruiting participants from populations seeking treatment in ordinary clinical practice settings.

Acknowledgments

The authors would like to thank Julian Higgins, Georgia Salanti and John Geddes for their helpful comments and feedback on the protocol. We would also like to thank Hugh McGuire for his assistance with this review.

CHARACTERISTICS OF STUDIES

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

Amini 2005

Methods	6 week randomised double blind study	
Participants	Diagnosis: DSM-IV major depressive disorder Setting: In- and outpatients	
Interventions	1. Mirtazapine: 30 mg/day, N = 18 2. Fluoxetine: 20 mg/day, N = 18 Fixed dosing scheduling	
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: None	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% of the participants dropped out and missing outcome data are balanced in numbers across intervention groups, with similar reasons of missing data across groups
Selective reporting (reporting bias)	Low risk	Both the response and the remission outcomes are reported in the figures with the actual numbers of the participants who achieved these
Free of Sponsorship bias?	Unclear risk	The funding source is not described.

Behnke 2003

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Unclear
Interventions	1. Mirtazapine: 30-45 mg/day, N = 176 2. Sertraline: 50-150 mg/day, N = 170 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-Improvement, CGI-Severity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	Both the response and the remission outcomes are reported in the figures with the actual numbers of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Benkert 2000

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 15-45 mg/day, N = 139 2. Paroxetine: 20-40 mg/day, N = 136 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: HAM-A, BDI, Welzil-Kohnen Colored Scales, Short Form-36, CGI-Improvement, CGI-severity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.

Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	Both the response and the remission outcomes at end of the acute-phase treatment are reported with the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Benkert 2006

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 45 mg/day, N = 130 2. Venlafaxine: 225 mg/day, N = 128 Fixed dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-Improvement, CGI-Severity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	Both the response and the remission outcomes at end of the acute-phase treatment are reported with the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Bremner 1995

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-III major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 5-35 mg/day, N = 50 2. Amitriptlyline: 40-280 mg/day, N = 50 3. Placebo, N = 50 Flexible dosing scheduling

Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-Improvement, CGI-Severity, Zung Self-Rating Depression Scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% of the participants dropped out and missing outcome data are balanced in numbers across intervention groups, with similar reasons of missing data across groups
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Brunnauer 2008

Methods	2 week randomised study
Participants	Diagnosis: DSM-IV major depressive disorder, single episode Setting: Psychiatric inpatients
Interventions	1. Mirtazapine: mean 38.2 (SD 9.0) mg/day, N = 20 2. Reboxetine: mean 6.6 (SD 1.9) mg/day, N = 20 Flexible dosing scheduling
Outcomes	The measure used for primary outcome: Performance in driving simulator Other measures: HAM-D, BDI
Notes	Only information about attrition of the participants is available for the present review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% of the participants dropped out and missing outcome data are balanced in numbers across intervention groups, with similar reasons of missing data across groups
Selective reporting (reporting bias)	Unclear risk	No useful information in terms of depression severity at the end of treatment is provide
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of the comparator drug

Debonnel 2000a

Methods	4 week randomised study
Participants	Diagnosis: DSM-IV major depression Setting: Unclear
Interventions	1. Mirtazapine: 30-45 mg/day, N = 20 2. Paroxetine: 20-30 mg/day, N = 20 3. Combination of mirtazapine and paroxetine Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: Unclear Other measures: MADRS
Notes	We were unable to retrieve usable information for the meta-analysis and to contact the author because the principal author passed away

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of attrition to permit judgement is provided.
Selective reporting (reporting bias)	Unclear risk	No information to permit judgement is provided.
Free of Sponsorship bias?	Unclear risk	No information to permit judgement is provided.

Fava 2006

Methods	14 week randomised study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 15-60 mg/day, N = 114 2. Nortriptyline: 25-150 mg/day, N = 121 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 16-item Quick Inventory of Depressive Symptomatology Other measures: 17-item HAM-D, Short-Form Health Survey, Work Productivity and Activity Impairment Questionnaire, Work and Social Adjustment Scale, Quality of Life Enjoyment and Satisfaction Questionnaire
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: “random assignment” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Comment: Both the participants and the clinicians knew the treatment status
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information of attrition to permit judgement is provided.
Selective reporting (reporting bias)	Low risk	Both the response and the remission outcomes are reported in figures with the proportion of the participants who achieved these
Free of Sponsorship bias?	Low risk	The funding source is National Institute of Mental Health.

Guelfi 2000

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Inpatients
Interventions	1. Mirtazapine: 45-60 mg/day, N = 78 2. Venlafaxine: 75-375 mg/day, N = 79 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: The Quality of Life, Enjoyment, and Satisfaction Questionnaire and Quality of Life in Depression Scale, Quality of Life in Depression Scales
Notes	

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “randomised” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: “participants were randomised to receive treatment with either mirtazapine or venlafaxine orally for 8 weeks, prepared as indistinguishable capsules, according to a centrally prepared randomization list” Comment: No further information about actual central randomisation provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind” Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	Both the response and the remission outcomes at end of the acute-phase treatment are reported with the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Halikas 1995

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-III major depressive disorder Setting: Outpatients over 55 years of age
Interventions	1. Mirtazapine: 5-35 mg/day, N = 50 2. Trazodone: 40-280 mg/day, N = 50 3. Placebo, N = 50 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 21-item HAM-D Other measures: MADRS, CGI-Severity, Zung Self-Rating Scale for Depression
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Hong 2003

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 15-40 mg/day, N = 66 2. Fluoxetine: 20-40 mg/day, N = 66 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: CGI-Severity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias)	Unclear risk	Quote: "double-blind" Comment: No further information provided.

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response and remission outcomes at the end of acute-phase treatment are provided as the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Hoyberg 1996

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-III major depressive disorder Setting: In- and outpatients
Interventions	1. Mirtazapine: 15-45 mg/day, N = 56 2. Amitriptyline: 30-90 mg/day, N = 59 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 21-item HAM-D Other measures: MADRS, CGI-Improvement, CGI-Severity, Brief Cognitive Rating Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to the mirtazapine arm dropped out during the study
Selective reporting (reporting bias)	High risk	Neither the response or remission outcomes at the end of acute-phase treatment are provided. They needed to be imputed in the analysis
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Leinonen 1999

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: In- and outpatients
Interventions	1. Mirtazapine: 15-40 mg/day, N = 66 2. Fluoxetine: 20-40 mg/day, N = 66 Flexiblie dosing scheduling
Outcomes	The measure used for response and remission in the review: MADRS

	Other measures: HAM-A, CGI-Improvement, CGI-Severity, Leeds Sleep Evaluation Questionnaire -adapted, Quality of Life Enjoyment and Satisfaction Questionnaire
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "participants were allocated to treatment with either mirtazapine or citalopram, according to the centrally prepared randomization list" Comment: No further information about actual central randomisation provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% of the participants dropped out and missing outcome data are balanced in numbers across intervention groups, with similar reasons of missing data across groups
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Marttila 1995

Methods	6 week randomised double blind study
Participants	Diagnosis: Research Diagnostic criteria major depressive disorder Setting: In- and outpatients
Interventions	1. Mirtazapine: 20-60 mg/day, N =83 2. Doxepin: 75-300 mg/day, N = 80 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, Brief Psychiatric Rating Scale, Global Assessment Score, Beck Depression Inventory, Newcastle Endogenous / Reactive Depression Rating Scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to the comparator arm dropped out during the study

Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Mullin 1996

Methods	5 week randomised double blind study	
Participants	Diagnosis: DSM-III major depressive disorder Setting: In- and outpatients	
Interventions	1. Mirtazapine: 20-60 mg/day, N = 79 2. Amitriptyline: 75-225 mg/day, N = 77 Flexible dosing scheduling	
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, Brief Psychiatric Rating Scale, General Assessment Scale	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to the comparator arm dropped out during the study
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Organon 85146

Methods	6 week randomised double blind study	
Participants	Diagnosis: DSM-III major depressive disorder Setting: Inpatients	
Interventions	1. Mirtazapine: 20-60 mg/day, N = 103 2. Amitriptyline: 75-225 mg/day, N = 104 Flexible dosing scheduling	
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-Improvement	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: “randomly allocated” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind” Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Richou 1995

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Inpatients
Interventions	1. Mirtazapine: 20-80 mg/day, N = 87 2. Clomipramine: 50-200 mg/day, N = 87 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 21-item HAM-D Other measures: MADRS, Brief Psychiatric Rating Scale, General Assessment Scale
Notes	

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “randomly allocated” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind” Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Schatzberg 2002

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients

Interventions	1. Mirtazapine: 15-40 mg/day, N = 128 2. Paroxetine: 20-40 mg/day, N = 126 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: CGI-Severity, CGI-Improvement
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The information of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to the comparator arm dropped out during the study
Selective reporting (reporting bias)	Low risk	The response and remission outcomes at the end of acute-phase treatment are provided as the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Schoemaker 2002

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 15-45 mg/day, N = 205 2. Fluvoxamine: 50-150 mg/day, N = 207 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: 21-item HAM-D
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to the comparator arm dropped out during the study
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this

Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Schule 2006

Methods	5 week randomised study
Participants	Diagnosis: DSM-IV major depressive episode (bipolar disorder not included) Setting: Psychiatric inpatients
Interventions	1. Mirtazapine: 45 mg/day, N = 20 2. Reboxetine: 8 mg/day, N = 20 Fixed dosing scheduling
Outcomes	The measure used for response and remission in the review: 21-item HAM-D Other measures: Hypothalamic-pituitary-adrenocortical axis activity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "We abstained from blinding the medication because the side effect profiles of reboxetine and mirtazapine markedly differ"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% of the participants dropped out and missing outcome data are balanced in numbers across intervention groups, with similar reasons of missing data across groups
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the numbers of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mir-tazapine

Smith 1990

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-III major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: −35 mg/day, N = 50 2. Amitriptyline: −280 mg/day, N = 50 3. Placebo, N = 50 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-Improvement, CGI-Severity, Zung Self-Rating Depression Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: “randomised” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind” Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The numbers of dropouts in the both arms are not specified.
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Thase 2000

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients
Interventions	1. Mirtazapine: 15-45 mg/day, N = 124 2. Sertraline: 50-200 mg/day, N = 126 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: Inventory of Depressive Symptomatology - Self-Report Scale, Social Adaptation Self-evaluation Scale, CGI-Severity, CGI-Efficacy
Notes	

Risk of bias

Bias	**Authors’ judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “randomised” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind” Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response and remission outcomes at the end of acute-phase treatment are provided as the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Turan 2000a

Methods	60 day randomised study

Participants	Diagnosis: DSM-IV major depressive disorder Setting: Unclear
Interventions	1. Mirtazapine: unclear dose, N = 25 2. Amitriptyline: unclear dose, N = 27 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-I
Notes	We were unable to retrieve usable information for the meta-analysis and to obtain replies from the author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information to permit judgement is provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% of the participants dropped out and missing outcome data are balanced in numbers across intervention groups, with similar reasons of missing data across groups
Selective reporting (reporting bias)	Unclear risk	No information to permit judgement is provided.
Free of Sponsorship bias?	Unclear risk	No information to permit judgement is provided.

van Moffaert 1995

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-III major depressive disorder Setting: Inpatients
Interventions	1. Mirtazapine: 24-72 mg/day, N = 100 2. Trazodone: 150-450 mg/day, N = 100 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, Brief Psychiatric Rating Scale, General Psychiatric Impression Global Assessment Scale, Beck Depression Inventory
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study

Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Versiani 2005

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: In- and outpatients
Interventions	1. Mirtazapine: 30-60 mg/day, N = 147 2. Fluoxetine: 20-40 mg/day, N = 152 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: MADRS, CGI-Severity, Leeds Sleep Evaluation Questionnaire, Quality of Life, Enjoyment and Satisfaction Questionnaire, Changes in Sezual Functioning Questionnaire
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The numbers of dropouts in the both arms are not specified.
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided in the figure as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Wade 2003

Methods	24 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Outpatients (in general practitioner clinics)
Interventions	1. Mirtazapine: 30-45 mg/day, N = 99 2. Paroxetine: 20-30 mg/day, N = 98 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: CGI-Improvement, CGI-Severity, CGI-Patient Global Evaluation

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomization was performed according to centrally prepared randomization lists" Comment: No further information about actual central randomization provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response and remission outcomes at the end of acute-phase treatment are provided in the figures as the proportion of the participants who achieved these
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Wheatley 1998

Methods	6 week randomised double blind study	
Participants	Diagnosis: DSM-III-R major depressive disorder Setting: In- and outpatients	
Interventions	1. Mirtazapine: 15-60 mg/day, N = 66 2. Fluoxetine: 20-40 mg/day, N = 67 Flexible dosing scheduling	
Outcomes	The measure used for response and remission in the review: 17-item HAM-D Other measures: CGI-Severity, the Visual Analogue Mood Rating Scale, Quality of Life Enjoyment and Satisfaction Questionnaire	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "participants were allocated to treatment with either mirtazapine or fluoxetine, according to the centrally prepared randomization list" Comment: No further information about actual central randomization provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response and remission outcomes at the end of acute-phase treatment are provided in the figures as the proportion of the participants who achieved these

Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Winokur 2003

Methods	8 week randomised double blind study
Participants	Diagnosis: DSM-IV major depressive disorder Setting: Unclear
Interventions	1. Mirtazapine: 45 mg/day, N = 9 2. Fluoxetine: 40 mg/day, N = 13 Fixed dosing scheduling
Outcomes	The measure used for response and remission in the review: 21-item HAM-D Other measures: CGI-Severity, polysomnographic data, multiple sleep latency testing, performance vigilance testing, Epworth Sleepiness Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned" Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to the comparator arm dropped out during the study
Selective reporting (reporting bias)	High risk	Neither the response nor remission outcomes at the end of acute-phase treatment are provided. They needed to be imputed in the analysis
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Zivkov 1995

Methods	6 week randomised double blind study
Participants	Diagnosis: DSM-III major depressive disorder Setting: Inpatients
Interventions	1. Mirtazapine: 20-60 mg/day, N = 125 2. Amitriptyline: 75-225 mg/day, N = 126 Flexible dosing scheduling
Outcomes	The measure used for response and remission in the review: 21-item HAM-D Other measures; Brief Psychiatric Rating Scale, General Assessment Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Unclear risk	Quote: “randomised” Comment: No further information provided.
Allocation concealment (selection bias)	Unclear risk	Comment: The method of allocation is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind” Comment: No further information provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 20% of the allocated participants to both of the intervention arms dropped out during the study
Selective reporting (reporting bias)	Low risk	The response outcome at the end of acute-phase treatment is provided as the proportion of the participants who achieved this
Free of Sponsorship bias?	High risk	The funding source is the pharmaceutical company of mirtazapine

Abbreviations: CGI = Clinical Global Impression, HAM-D = Hamilton Rating Scale for Depression, MADRS =Montgomery-Asberg Depression Rating Scale, RDC = Research Diagnostic Criteria

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

Study	Reason for exclusion
Blier 2004	Mirtazapine was combined with another antidepressant.
Bruijin 1996	A review of other studies.
Kasper 1997a	A review of other studies.
Kasper 1997b	A review of other studies.
Kremer 1995	Not a relevant diagnostic status.
Peyron 1996	Not a relevant diagnostic status.
Tulen 1996	Not a relevant diagnostic status.
Zourkova 2001	Not employing random allocation.

DATA AND ANALYSES

Comparison 1
Mirtazapine versus TCAs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome (response) at 2 weeks	8	1294	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.13]
1.1 vs Amitriptyline	5	722	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.54, 1.12]
1.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.46, 1.73]
1.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.58, 2.12]
1.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.22, 3.22]
2 Primary outcome (response) at end of the acute-phase treatment	9	1501	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.72, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 vs Amitriptyline	6	929	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.69, 1.17]
2.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.71]
2.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.44, 1.63]
2.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.55]
3 Secondary outcome (remission) at 2 weeks	8	1294	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.55, 1.32]
3.1 vs Amitriptyline	5	722	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.35, 1.29]
3.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.34, 2.31]
3.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.54, 3.00]
3.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.12, 4.28]
4 Secondary outcome (remission) at end of the acute-phase treatment	9	1501	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.69, 1.08]
4.1 vs Amitriptyline	6	929	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.65, 1.16]
4.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.41, 1.45]
4.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.50, 1.74]
4.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.56]
5 Secondary outcome (depression severity) at 2 weeks	2	361	Std. Mean Difference (IV, Random, 95% CI)	0.10 [−0.11, 0.31]
5.1 vs Amitritpyline	2	361	Std. Mean Difference (IV, Random, 95% CI)	0.10 [−0.11, 0.31]
6 Secondary outcome (depression severity) at end of the acute-phase treatment	1	144	Std. Mean Difference (IV, Random, 95% CI)	0.12 [−0.21, 0.45]
6.1 vs Amitritpyline	1	144	Std. Mean Difference (IV, Random, 95% CI)	0.12 [−0.21, 0.45]
7 Secondary outcome (Social adjustment) at 2 weeks	1	138	Mean Difference (IV, Random, 95% CI)	1.60 [−1.98, 5.18]
7.1 vs Amitriptyline	1	138	Mean Difference (IV, Random, 95% CI)	1.60 [−1.98, 5.18]
8 Secondary outcome (Social adjustment) at end of the acute-phase treatment	3	440	Std. Mean Difference (IV, Random, 95% CI)	0.02 [−0.17, 0.21]
8.1 vs Amitriptyline	1	114	Std. Mean Difference (IV, Random, 95% CI)	0.03 [−0.34, 0.40]
8.2 vs Clomipramine	1	163	Std. Mean Difference (IV, Random, 95% CI)	0.12 [−0.19, 0.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 vs Doxepin	1	163	Std. Mean Difference (IV, Random, 95% CI)	−0.09 [−0.39, 0.22]
9 Secondary outcome (withdrawal due to any reason)	7	1166	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.63, 1.10]
9.1 vs Amitriptyline	5	829	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.65, 1.25]
9.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.54]
9.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.22, 1.19]
10 Secondary outcome (withdrawal due to adverse events)	8	1266	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.41, 1.03]
10.1 vs Amitriptyline	6	929	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.03]
10.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.42, 3.10]
10.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	0.30 [0.06, 1.56]
11 Secondary outcome (having some adverse events)	2	442	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.54, 2.10]
11.1 vs Amitriptyline	1	207	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.16, 3.37]
11.2 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.55, 2.49]
12 Hypertension/Tachycardia	4	522	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.24, 0.81]
12.1 vs Amitriptyline	4	522	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.24, 0.81]
13 Hypotension/Bradycardia	2	215	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.12, 1.81]
13.1 vs Amitriptyline	2	215	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.12, 1.81]
14 Sweating	2	458	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.05, 3.24]
14.1 vs Amitriptyline	2	458	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.05, 3.24]
15 Constipation	6	1003	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.46, 1.12]
15.1 vs Amitriptyline	5	829	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.40, 1.29]
15.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.26, 1.48]
16 Dry mouth/Decreased salivation	8	1266	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.24, 1.14]
16.1 vs Amitriptyline	6	929	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.14, 0.92]
16.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.39, 1.69]
16.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	2.86 [1.18, 6.94]
17 Nausea/Vomiting/Gastric distress	4	581	Odds Ratio (M-H, Random, 95% CI)	0.29 [0.05, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 vs Amitriptyline	3	407	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.04, 2.59]
17.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.33]
18 Weight gain/Increased appetite	3	463	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.58, 1.86]
18.1 vs Amitriptyline	3	463	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.58, 1.86]
19 Sexual dysfunction	2	351	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.61]
19.1 vs Amitriptyline	2	351	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.06, 2.61]
20 Anxiety/Agitation	2	307	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.34, 2.19]
20.1 vs Amitriptyline	2	307	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.34, 2.19]
21 Dizziness/Vertigo/Faintness	7	1166	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.43, 1.28]
21.1 vs Amitriptyline	5	829	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.35, 1.17]
21.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.21, 2.29]
21.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	3.04 [0.59, 15.53]
22 Fatigue/Tiredness/Asthenia	4	673	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.71, 2.21]
22.1 vs Amitriptyline	4	673	Odds Ratio (M-H, Random, 95% CI)	1.25 [0.71, 2.21]
23 Headache	4	522	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.31, 1.74]
23.1 vs Amitriptyline	4	522	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.31, 1.74]
24 Tremor	7	1103	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.22, 0.57]
24.1 vs Amitriptyline	6	929	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.20, 0.62]
24.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.15, 0.88]
25 Sleep disturbance	1	207	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.69, 2.98]
25.1 vs Amitriptyline	1	207	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.69, 2.98]
26 Sleepiness/Drowsiness/Somnolence	6	841	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.66, 1.27]
26.1 vs Amitriptyline	5	678	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.14]
26.2 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	1.86 [0.82, 4.21]
27 Suicide attempt	5	935	Odds Ratio (M-H, Random, 95% CI)	1.77 [0.47, 6.58]
27.1 vs Amitriptyline	2	363	Odds Ratio (M-H, Random, 95% CI)	2.08 [0.27, 16.29]
27.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 16.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 7.91]
27.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	9.90 [0.53, 185.90]
28 Subgroup analysis: Response at 2 weeks: Treatment settings: Psychiatric inpatients	2	425	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.50, 1.32]
28.1 vs Amitriptyline	1	251	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.36, 1.48]
28.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.46, 1.73]
29 Subgroup analysis: Response at end of the acute-phase treatment: Treatment settings: Psychiatric inpatients	3	632	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.23]
29.1 vs Amitriptyline	2	458	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.60, 1.29]
29.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.71]
30 Sensitivity analysis: Response at 2 weeks: Studies without imputation	7	1179	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.15]
30.1 vs Amitriptyline	4	607	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.13]
30.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.46, 1.73]
30.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.58, 2.12]
30.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.22, 3.22]
31 Sensitivity analysis: Response at end of the acute-phase treatment: Studies without imputation	8	1386	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.15]
31.1 vs Amitriptyline	5	814	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
31.2 vs Clomipramine	1	174	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.71]
31.3 vs Doxepin	1	163	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.44, 1.63]
31.4 vs Nortriptyline	1	235	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.55]
32 Secondary outcome (SKEWED DATA: depression severity) at 2 weeks			Other data	No numeric data
33 Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment			Other data	No numeric data

Comparison 2
Mirtazapine versus SSRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome (response) at 2 weeks	12	2626	Odds Ratio (M-H, Random, 95% CI)	1.57 [1.30, 1.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	2.01 [0.93, 4.35]
1.2 vs Fluoxetine	5	622	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.86, 1.85]
1.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	2.39 [1.42, 4.02]
1.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.45 [1.04, 2.02]
1.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.90, 2.13]
2 Primary outcome (response) at end of the acute-phase treatment	12	2626	Odds Ratio (M-H, Random, 95% CI)	1.19 [1.01, 1.39]
2.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.38, 1.52]
2.2 vs Fluoxetine	5	622	Odds Ratio (M-H, Random, 95% CI)	1.55 [1.07, 2.23]
2.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.94, 1.70]
2.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.70, 1.35]
2.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.76, 1.70]
3 Primary outcome (response) at end of the continuation treatment	1	197	Odds Ratio (M-H, Random, 95% CI)	1.60 [0.91, 2.81]
3.1 vs Paroxetine	1	197	Odds Ratio (M-H, Random, 95% CI)	1.60 [0.91, 2.81]
4 Secondary outcome (remission) at 2 weeks	12	2626	Odds Ratio (M-H, Random, 95% CI)	1.82 [1.36, 2.44]
4.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	2.48 [0.47, 13.02]
4.2 vs Fluoxetine	5	622	Odds Ratio (M-H, Random, 95% CI)	1.63 [0.81, 3.27]
4.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	2.31 [1.04, 5.11]
4.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.94 [1.19, 3.15]
4.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.77, 2.76]
5 Secondary outcome (remission) at end of the acute-phase treatment	12	2626	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.98, 1.40]
5.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.55, 1.52]
5.2 vs Fluoxetine	5	622	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.80, 1.57]
5.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	1.58 [1.16, 2.15]
5.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.82, 1.71]
5.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.57, 1.23]
6 Secondary outcome (remission) at end of the continuation treatment	1	197	Odds Ratio (M-H, Random, 95% CI)	1.89 [1.01, 3.54]
6.1 vs Paroxetine	1	197	Odds Ratio (M-H, Random, 95% CI)	1.89 [1.01, 3.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Secondary outcome (withdrawal due to any reason)	11	2327	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.89, 1.40]
7.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	2.36 [0.99, 5.64]
7.2 vs Fluoxetine	4	323	Odds Ratio (M-H, Random, 95% CI)	1.09 [0.67, 1.78]
7.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.10]
7.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.47 [1.01, 2.13]
7.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.75, 1.93]
8 Secondary outcome (withdrawal due to adverse events)	11	2604	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.85, 1.86]
8.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	2.0 [0.59, 6.81]
8.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.62, 1.78]
8.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.45, 1.21]
8.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	2.88 [1.43, 5.77]
8.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.66 [0.86, 3.21]
9 Secondary outcome (having some adverse events)	7	1773	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.81, 1.26]
9.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.49, 1.37]
9.2 vs Fluoxetine	2	431	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.97, 2.09]
9.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.66, 1.32]
9.4 vs Sertraline	1	346	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.55, 1.34]
10 Hypotension/Bradycardia	1	133	Odds Ratio (M-H, Random, 95% CI)	5.41 [0.61, 47.62]
10.1 vs Fluoxetine	1	133	Odds Ratio (M-H, Random, 95% CI)	5.41 [0.61, 47.62]
11 Sweating	5	1342	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.15, 0.44]
11.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.13 [0.04, 0.44]
11.2 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.62]
11.3 vs Sertraline	1	346	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.04, 0.97]
12 Constipation	5	1109	Odds Ratio (M-H, Random, 95% CI)	1.20 [0.79, 1.82]
12.1 vs Fluoxetine	2	168	Odds Ratio (M-H, Random, 95% CI)	2.14 [0.81, 5.66]
12.2 vs Paroxetine	2	529	Odds Ratio (M-H, Random, 95% CI)	1.07 [0.59, 1.95]
12.3 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.48, 2.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Diarrhoea	8	2040	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.41, 0.80]
13.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.14, 1.60]
13.2 vs Fluoxetine	1	36	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 17.33]
13.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.46]
13.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.21, 0.67]
13.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.13, 0.87]
14 Dry mouth/Decreased salivation	10	2305	Odds Ratio (M-H, Random, 95% CI)	1.80 [1.37, 2.36]
14.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	1.72 [0.81, 3.68]
14.2 vs Fluoxetine	3	301	Odds Ratio (M-H, Random, 95% CI)	3.68 [1.52, 8.91]
14.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	1.73 [0.81, 3.70]
14.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.53 [0.92, 2.55]
14.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.48 [0.77, 2.85]
15 Nausea/Vomiting/Gastric distress	11	2604	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.26, 0.43]
15.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.45 [0.22, 0.90]
15.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.14, 0.81]
15.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.16, 0.44]
15.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.16, 0.48]
15.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.29 [0.16, 0.53]
16 Weight gain/Increased appetite	11	2604	Odds Ratio (M-H, Random, 95% CI)	4.23 [2.93, 6.11]
16.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	3.83 [1.49, 9.82]
16.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	5.23 [2.15, 12.76]
16.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	3.92 [1.19, 12.92]
16.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	6.67 [3.30, 13.49]
16.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	2.51 [0.87, 7.26]
17 Weight loss/Anorexia	4	576	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.10, 1.18]
17.1 vs Fluoxetine	3	301	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.11, 1.62]
17.2 vs Paroxetine	1	275	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Sexual dysfunction	4	907	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.13, 0.74]
18.1 vs Fluoxetine	1	36	Odds Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.47]
18.2 vs Paroxetine	1	275	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.06, 0.59]
18.3 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.10, 1.82]
19 Anxiety/Agitation	4	1134	Odds Ratio (M-H, Random, 95% CI)	1.46 [0.59, 3.65]
19.1 vs Paroxetine	2	472	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.32, 1.60]
19.2 vs Sertraline	1	250	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.69, 3.98]
19.3 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	5.76 [1.65, 20.07]
20 Dizziness/Vertigo/Faintness	10	2568	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.77, 1.41]
20.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	2.03 [0.74, 5.58]
20.2 vs Fluoxetine	3	564	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.54, 1.56]
20.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.50]
20.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.16 [0.36, 3.70]
20.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.31 [0.69, 2.48]
21 Fatigue/Tiredness/Asthenia	8	2137	Odds Ratio (M-H, Random, 95% CI)	1.53 [1.08, 2.15]
21.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.44, 1.84]
21.2 vs Fluoxetine	1	133	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.30, 6.40]
21.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	1.71 [0.94, 3.11]
21.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	2.31 [1.32, 4.04]
21.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.44, 2.00]
22 Headache	11	2604	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.56, 0.86]
22.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.33]
22.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.54, 1.36]
22.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.36, 0.89]
22.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.67 [0.44, 1.01]
22.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.46, 1.53]
23 Tremor	5	996	Odds Ratio (M-H, Random, 95% CI)	0.34 [0.18, 0.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 vs Fluoxetine	3	467	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.17, 1.07]
23.2 vs Paroxetine	2	529	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.70]
24 Sleep disturbance	5	1346	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.31, 0.86]
24.1 vs Fluoxetine	1	299	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.21, 1.38]
24.2 vs Paroxetine	2	451	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.25, 1.85]
24.3 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.16, 0.85]
25 Sleepiness/Drowsiness/Somnolence	11	2604	Odds Ratio (M-H, Random, 95% CI)	1.81 [1.39, 2.37]
25.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.53, 3.51]
25.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	1.59 [0.97, 2.61]
25.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.84, 1.83]
25.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	3.07 [1.89, 4.99]
25.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	2.34 [1.45, 3.77]
26 Suicide attempt	1	346	Odds Ratio (M-H, Random, 95% CI)	4.89 [0.23, 102.51
26.1 vs Sertraline	1	346	Odds Ratio (M-H, Random, 95% CI)	4.89 [0.23, 102.51
27 Subgroup analysis: Response at 2 weeks: Treatment settings: Outpatients in primary care	1	197	Odds Ratio (M-H, Random, 95% CI)	4.38 [1.69, 11.35]
27.1 vs Paroxetine	1	197	Odds Ratio (M-H, Random, 95% CI)	4.38 [1.69, 11.35]
28 Subgroup analysis: Response at end of the acute-phase treatment: Treatment settings: Outpatients in primary care	1	197	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.66, 2.10]
28.1 vs Paroxetine	1	197	Odds Ratio (M-H, Random, 95% CI)	1.17 [0.66, 2.10]
29 Sensitivity analysis: Response at 2 weeks: Studies without imputation	11	2604	Odds Ratio (M-H, Random, 95% CI)	1.58 [1.31, 1.90]
29.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	2.01 [0.93, 4.35]
29.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.86, 1.88]
29.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	2.39 [1.42, 4.02]
29.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	1.45 [1.04, 2.02]
29.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.90, 2.13]
30 Sensitivity analysis: Response at end of the acute-phase treatment: Studies without imputation	11	2604	Odds Ratio (M-H, Random, 95% CI)	1.17 [1.00, 1.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30.1 vs Citalolpram	1	270	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.38, 1.52]
30.2 vs Fluoxetine	4	600	Odds Ratio (M-H, Random, 95% CI)	1.46 [1.04, 2.04]
30.3 vs Paroxetine	3	726	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.94, 1.70]
30.4 vs Sertraline	2	596	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.70, 1.35]
30.5 vs Fluvoxamine	1	412	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.76, 1.70]
31 Secondary outcome (SKEWED DATA: depression severity) at 2 weeks			Other data	No numeric data
32 Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment			Other data	No numeric data

Comparison 3
Mirtazapine versus SNRIs

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome (response) at 2 weeks	2	415	Odds Ratio (M-H, Random, 95% CI)	2.29 [1.45, 3.59]
1.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	2.29 [1.45, 3.59]
2 Primary outcome (response) at end of the acute-phase treatment	2	415	Odds Ratio (M-H, Random, 95% CI)	1.53 [1.03, 2.25]
2.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	1.53 [1.03, 2.25]
3 Secondary outcome (remission) at 2 weeks	2	415	Odds Ratio (M-H, Random, 95% CI)	2.34 [1.07, 5.13]
3.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	2.34 [1.07, 5.13]
4 Secondary outcome (remission) at end of the acute-phase treatment	2	415	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.98, 2.47]
4.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	1.55 [0.98, 2.47]
5 Secondary outcome (withdrawal due to any reason)	2	415	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.43, 0.99]
5.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.43, 0.99]
6 Secondary outcome (withdrawal due to adverse events)	2	415	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.24, 1.24]
6.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.24, 1.24]
7 Secondary outcome (having some adverse events)	1	157	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.76, 3.00]
7.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.76, 3.00]
8 Hypotension/Bradycardia	1	157	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.68]
9 Sweating	1	157	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.45]
9.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.00, 0.45]
10 Constipation	1	157	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.83]
10.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.06, 0.83]
11 Dry mouth/Decreased salivation	2	415	Odds Ratio (M-H, Random, 95% CI)	8.61 [0.35, 211.85]
11.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	8.61 [0.35, 211.85]
12 Nausea/Vomiting/Gastric distress	2	415	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.00, 9.34]
12.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	0.11 [0.00, 9.34]
13 Anxiety/Agitation	1	157	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.24, 4.20]
13.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.24, 4.20]
14 Fatigue/Tiredness/Asthenia	1	258	Odds Ratio (M-H, Random, 95% CI)	2.43 [1.30, 4.55]
14.1 vs Venlafaxine	1	258	Odds Ratio (M-H, Random, 95% CI)	2.43 [1.30, 4.55]
15 Headache	2	415	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.72]
15.1 vs Venlafaxine	2	415	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.72]
16 Sleep disturbance	1	258	Odds Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.41]
16.1 vs Venlafaxine	1	258	Odds Ratio (M-H, Random, 95% CI)	0.02 [0.00, 0.41]
17 Sleepiness/Drowsiness/Somnolence	1	157	Odds Ratio (M-H, Random, 95% CI)	1.56 [0.42, 5.77]
17.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	1.56 [0.42, 5.77]
18 Completed suicide	1	157	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.31]
18.1 vs Venlafaxine	1	157	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.31]

Comparison 4
Mirtazapine versus heterocyclic antidepressants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome (response) at 2 weeks	2	300	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.64, 2.04]
1.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.64, 2.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Primary outcome (response) at end of the acute-phase treatment	2	300	Odds Ratio (M-H, Random, 95% CI)	1.50 [0.95, 2.37]
2.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	1.50 [0.95, 2.37]
3 Secondary outcome (remission) at 2 weeks	2	300	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.36, 2.80]
3.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.36, 2.80]
4 Secondary outcome (remission) at end of the acute-phase treatment	2	300	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.76, 2.52]
4.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.76, 2.52]
5 Secondary outcome (withdrawal due to any reason)	2	300	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.72]
5.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.47, 1.72]
6 Secondary outcome (withdrawal due to adverse events)	2	300	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.25, 1.51]
6.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.25, 1.51]
7 Hypertension/Tachycardia	1	100	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.59]
7.1 vs Trazodone	1	100	Odds Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.59]
8 Hypotension/Bradycardia	2	300	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.03, 1.00]
8.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.03, 1.00]
9 Constipation	1	100	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.26, 1.83]
9.1 vs Trazodone	1	100	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.26, 1.83]
10 Dry mouth/Decreased salivation	2	300	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.11, 1.37]
10.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.39 [0.11, 1.37]
11 Nausea/Vomiting/Gastric distress	1	100	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.20, 2.32]
11.1 vs Trazodone	1	100	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.20, 2.32]
12 Weight gain/Increased appetite	1	100	Odds Ratio (M-H, Random, 95% CI)	4.95 [1.30, 18.81]
12.1 vs Trazodone	1	100	Odds Ratio (M-H, Random, 95% CI)	4.95 [1.30, 18.81]
13 Weight loss/Anorexia	1	100	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.21]
13.1 vs Trazodone	1	100	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.01, 8.21]
14 Anxiety/Agitation	2	300	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.19, 1.96]
14.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.19, 1.96]
15 Dizziness/Vertigo/Faintness	2	300	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.30, 1.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.30, 1.39]
16 Headache	1	100	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.23, 1.87]
16.1 vs Trazodone	1	100	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.23, 1.87]
17 Sleep disturbance	1	200	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.13, 1.42]
17.1 vs Trazodone	1	200	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.13, 1.42]
18 Sleepiness/Drowsiness/Somnolence	2	300	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.29, 1.36]
18.1 vs Trazodone	2	300	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.29, 1.36]
19 Completed suicide	1	200	Odds Ratio (M-H, Random, 95% CI)	3.03 [0.12, 75.28]
19.1 vs Trazodone	1	200	Odds Ratio (M-H, Random, 95% CI)	3.03 [0.12, 75.28]
20 Suicide attempt	1	200	Odds Ratio (M-H, Random, 95% CI)	2.02 [0.18, 22.65]
20.1 vs Trazodone	1	200	Odds Ratio (M-H, Random, 95% CI)	2.02 [0.18, 22.65]

Comparison 5
Mirtazapine versus newer antidepressants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome (response) at 2 weeks	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.18, 5.67]
1.1 vs Reboxetine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.18, 5.67]
2 Primary outcome (response) at end of the acute-phase treatment	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.27, 3.67]
2.1 vs Reboxetine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.27, 3.67]
3 Secondary outcome (remission) at 2 weeks	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 17.18]
3.1 vs Reboxetine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 17.18]
4 Secondary outcome (remission) at end of the acute-phase treatment	1	40	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.33, 4.73]
4.1 vs Reboxetine	1	40	Odds Ratio (M-H, Random, 95% CI)	1.26 [0.33, 4.73]
5 Secondary outcome (depression severity) at 2 weeks	1	40	Std. Mean Difference (IV, Random, 95% CI)	−0.37 [−1.00, 0.25]
5.1 vs Reboxetine	1	40	Std. Mean Difference (IV, Random, 95% CI)	−0.37 [−1.00, 0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Secondary outcome (withdrawal due to any reason)	2	80	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.1 vs Reboxetine	2	80	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Secondary outcome (withdrawal due to adverse events)	2	80	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.1 vs Reboxetine	2	80	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment			Other data	No numeric data

Comparison 6
Funnel plot analysis: primary outcome (response) at end of the acute-phase treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 vs all compounds	26	4882	Risk Ratio (M-H, Fixed, 99% CI)	1.05 [0.99, 1.12]
1.1 vs Amitriptyline	6	929	Risk Ratio (M-H, Fixed, 99% CI)	0.95 [0.82, 1.11]
1.2 vs Clomipramine	1	174	Risk Ratio (M-H, Fixed, 99% CI)	0.97 [0.74, 1.26]
1.3 vs Doxepin	1	163	Risk Ratio (M-H, Fixed, 99% CI)	0.95 [0.71, 1.26]
1.4 vs Nortriptyline	1	235	Risk Ratio (M-H, Fixed, 99% CI)	0.94 [0.59, 1.49]
1.5 vs Citalolpram	1	270	Risk Ratio (M-H, Fixed, 99% CI)	0.96 [0.85, 1.09]
1.6 vs Fluoxetine	5	622	Risk Ratio (M-H, Fixed, 99% CI)	1.18 [1.00, 1.39]
1.7 vs Paroxetine	3	726	Risk Ratio (M-H, Fixed, 99% CI)	1.13 [0.93, 1.38]
1.8 vs Sertraline	2	596	Risk Ratio (M-H, Fixed, 99% CI)	0.99 [0.83, 1.17]
1.9 vs Fluvoxamine	1	412	Risk Ratio (M-H, Fixed, 99% CI)	1.05 [0.86, 1.28]
1.10 vs Venlafaxine	2	415	Risk Ratio (M-H, Fixed, 99% CI)	1.24 [0.96, 1.60]
1.11 vs Trazodone	2	300	Risk Ratio (M-H, Fixed, 99% CI)	1.21 [0.91, 1.61]
1.12 vs Reboxetine	1	40	Risk Ratio (M-H, Fixed, 99% CI)	1.0 [0.55, 1.82]

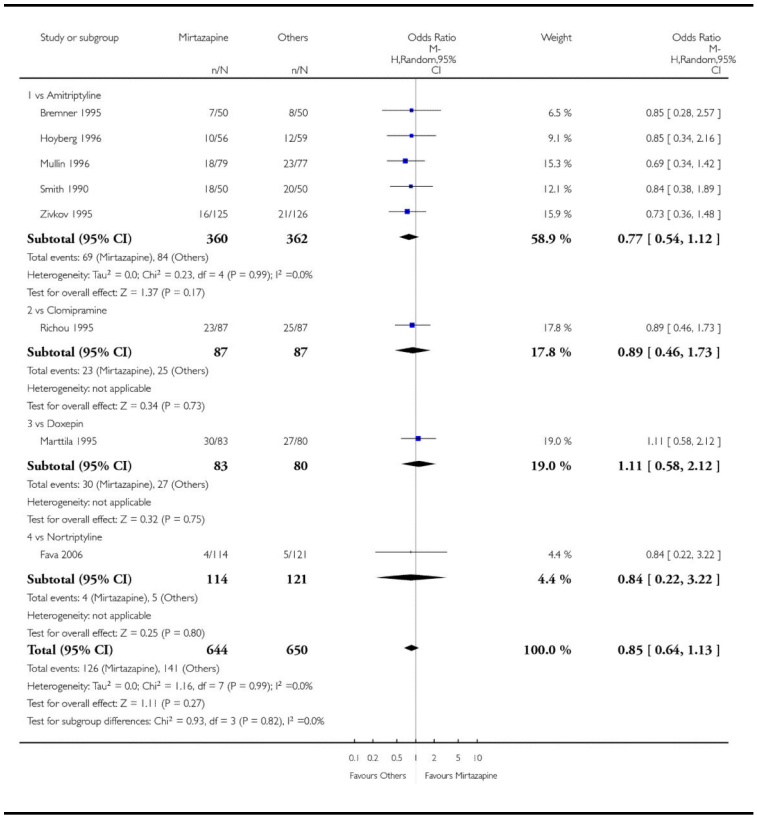
Analysis 1.1

Comparison 1 Mirtazapine versus TCAs, Outcome 1 Primary outcome (response) at 2 weeks

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 1 Primary outcome (response) at 2 weeks



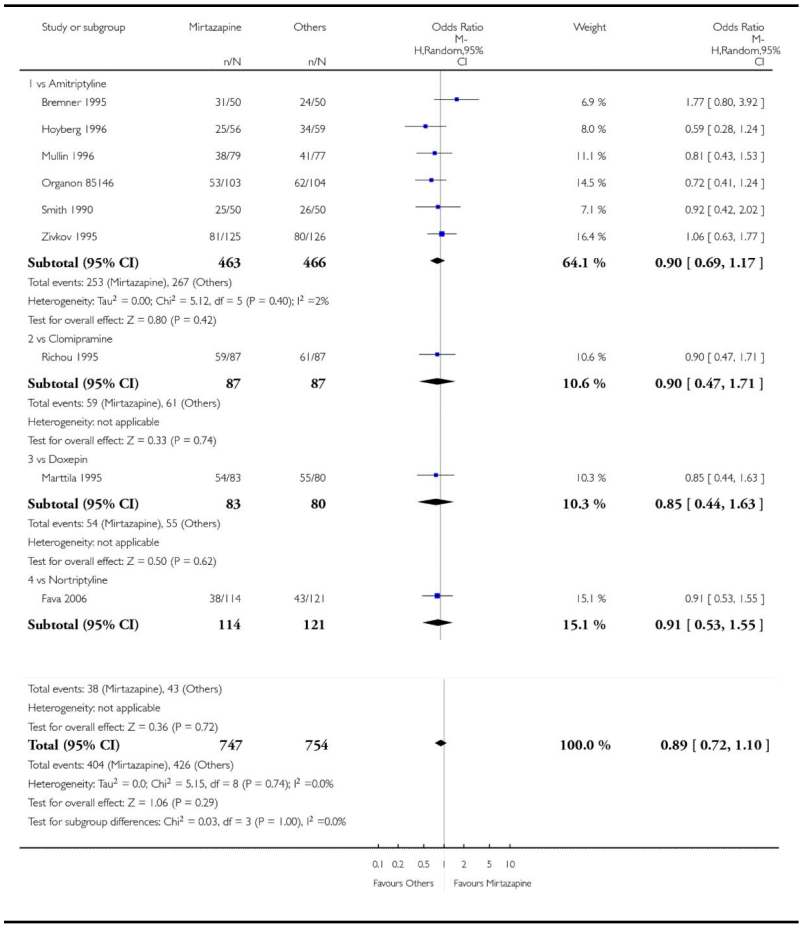
Analysis 1.2

Comparison 1 Mirtazapine versus TCAs, Outcome 2 Primary outcome (response) at end of the acute-phase treatment

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 2 Primary outcome (response) at end of the acute-phase treatment



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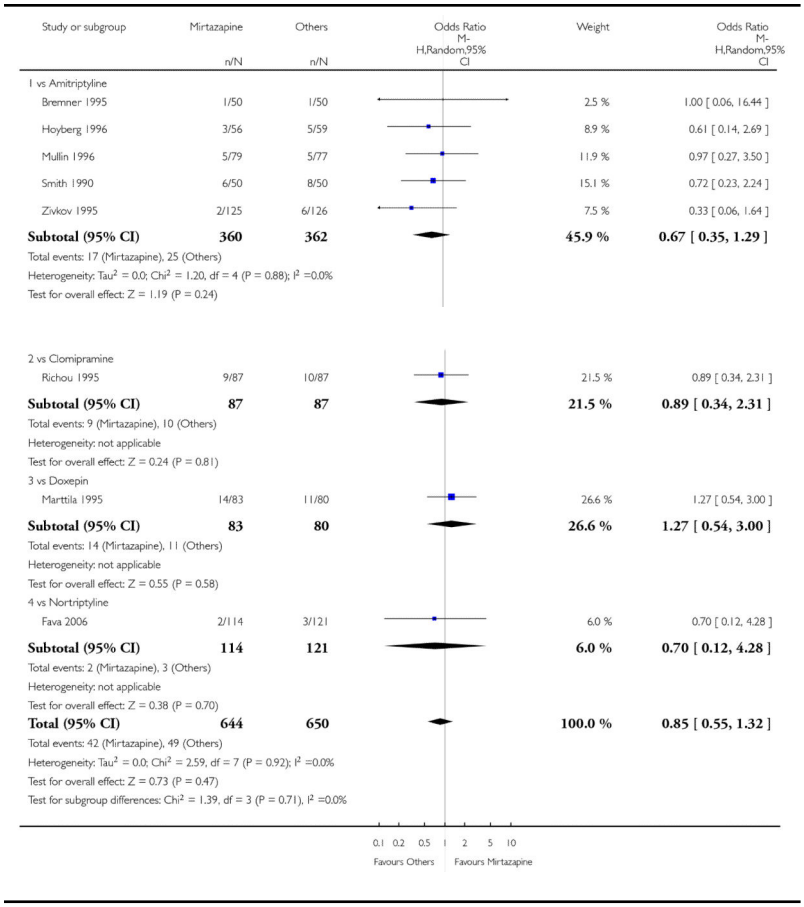
Analysis 1.3
Comparison 1 Mirtazapine versus TCAs, Outcome 3 Secondary outcome (remission) at 2 weeks

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 3 Secondary outcome (remission) at 2 weeks



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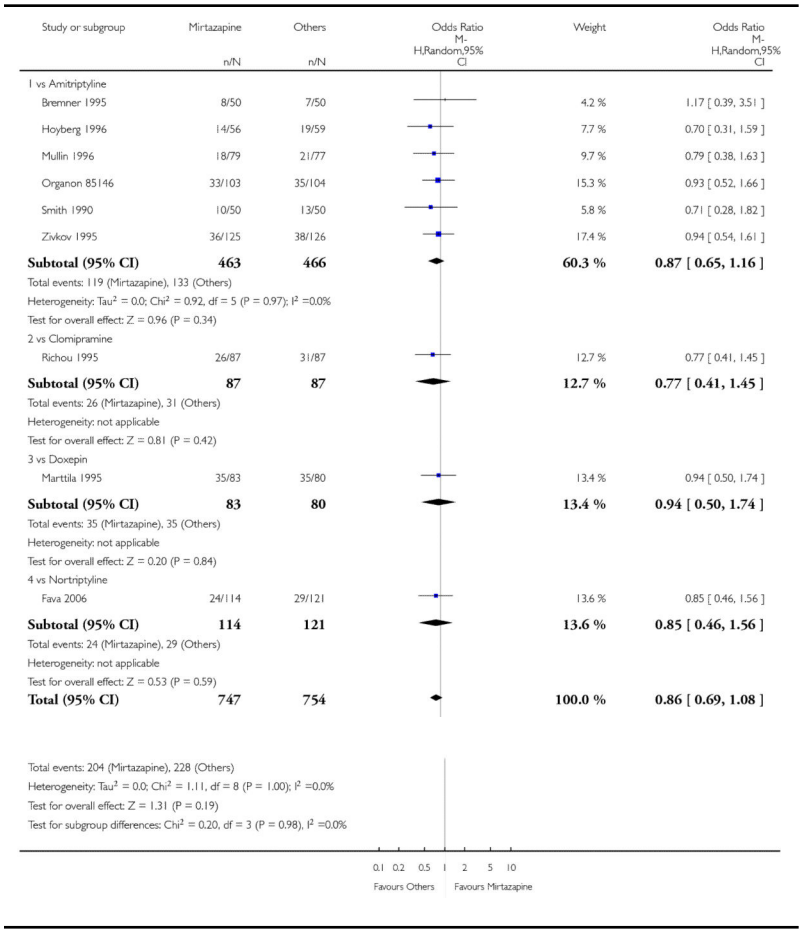
Analysis 1.4

Comparison 1 Mirtazapine versus TCAs, Outcome 4 Secondary outcome (remission) at end of the acute-phase treatment

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

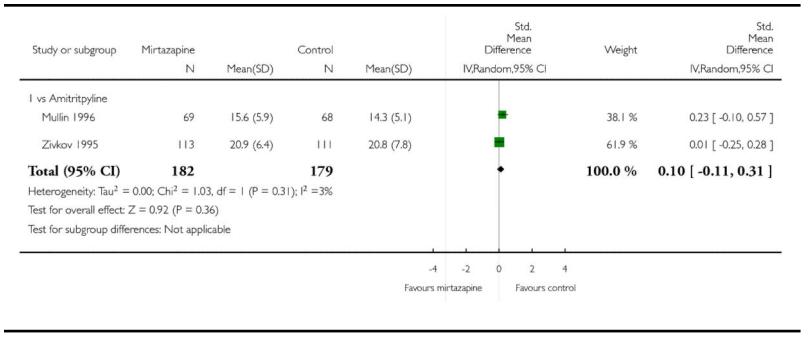
Outcome: 4 Secondary outcome (remission) at end of the acute-phase treatment



Analysis 1.5

Comparison 1 Mirtazapine versus TCAs, Outcome 5 Secondary outcome (depression severity) at 2 weeks

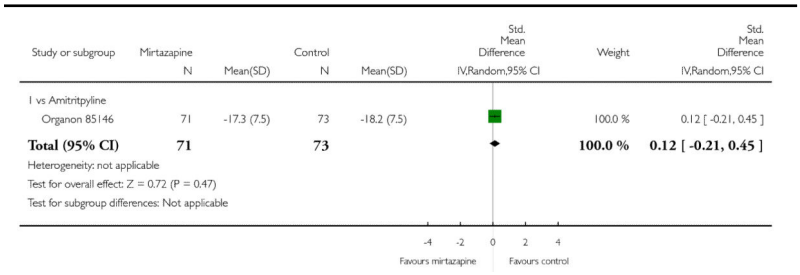
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 5 Secondary outcome (depression severity) at 2 weeks



Analysis 1.6

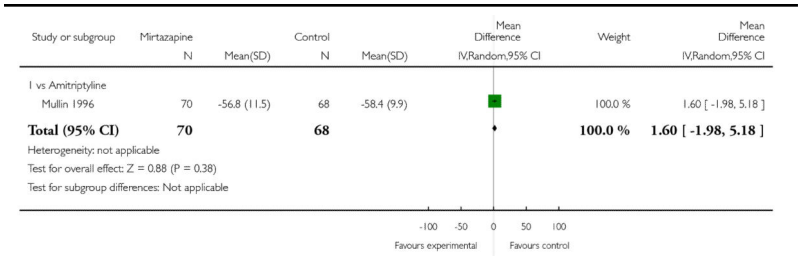
Comparison 1 Mirtazapine versus TCAs, Outcome 6 Secondary outcome (depression severity) at end of the acute-phase treatment

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 6 Secondary outcome (depression severity) at end of the acute-phase treatment



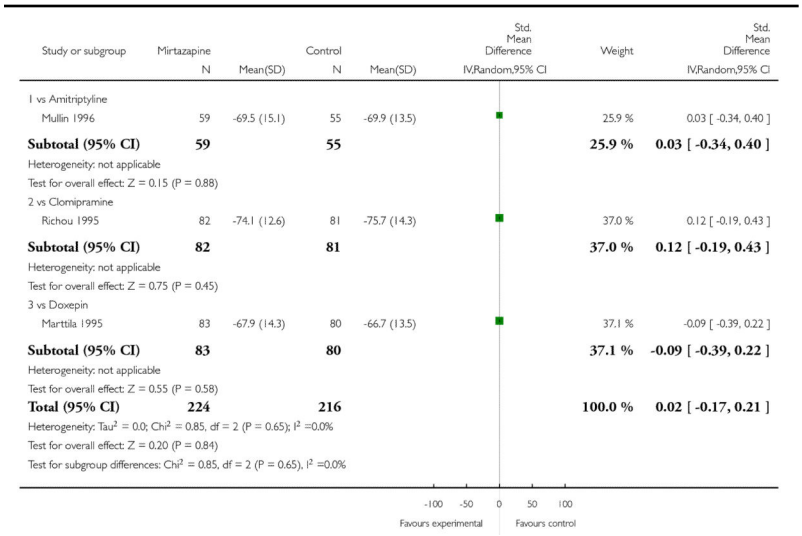
Analysis 1.7
Comparison 1 Mirtazapine versus TCAs, Outcome 7 Secondary outcome (Social adjustment) at 2 weeks

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 7 Secondary outcome (Social adjustment) at 2 weeks



Analysis 1.8
Comparison 1 Mirtazapine versus TCAs, Outcome 8 Secondary outcome (Social adjustment) at end of the acute-phase treatment

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 8 Secondary outcome (Social adjustment) at end of the acute-phase treatment



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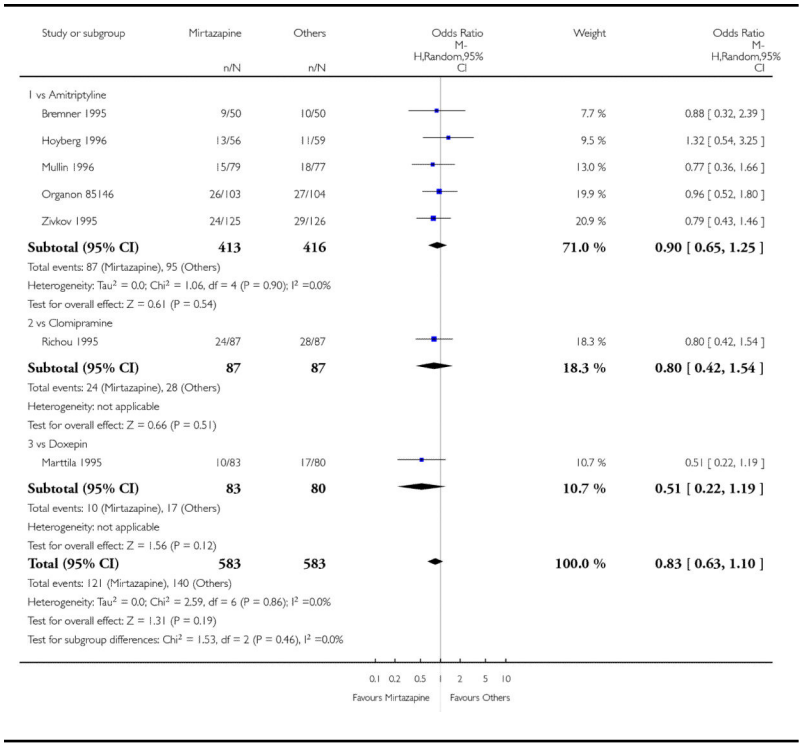
Analysis 1.9

Comparison 1 Mirtazapine versus TCAs, Outcome 9 Secondary outcome (withdrawal due to any reason)

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 9 Secondary outcome (withdrawal due to any reason)



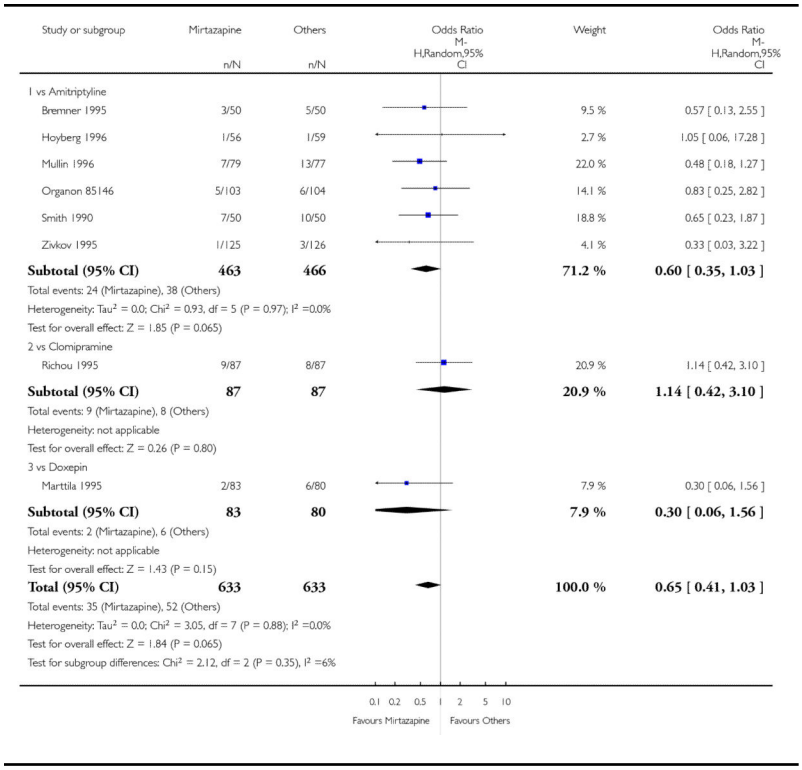
Analysis 1.10

Comparison 1 Mirtazapine versus TCAs, Outcome 10 Secondary outcome (withdrawal due to adverse events)

Review: Mirtazapine versus other antidepressive agents for depression

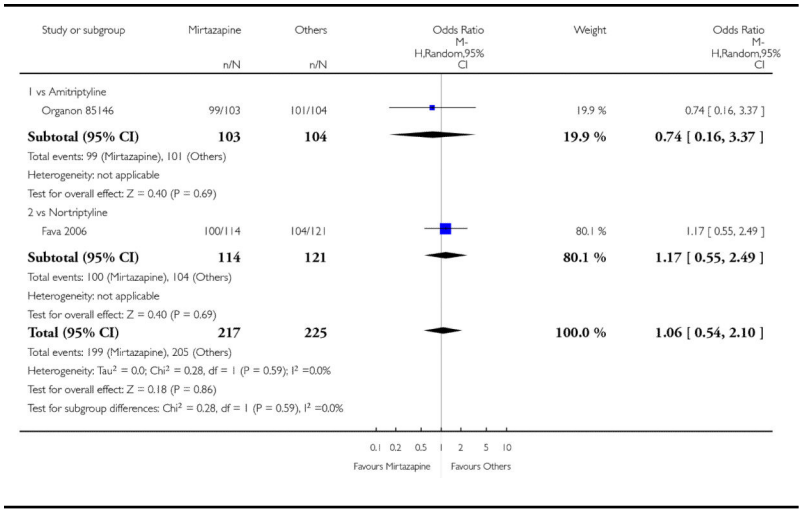
Comparison: 1 Mirtazapine versus TCAs

Outcome: 10 Secondary outcome (withdrawal due to adverse events)



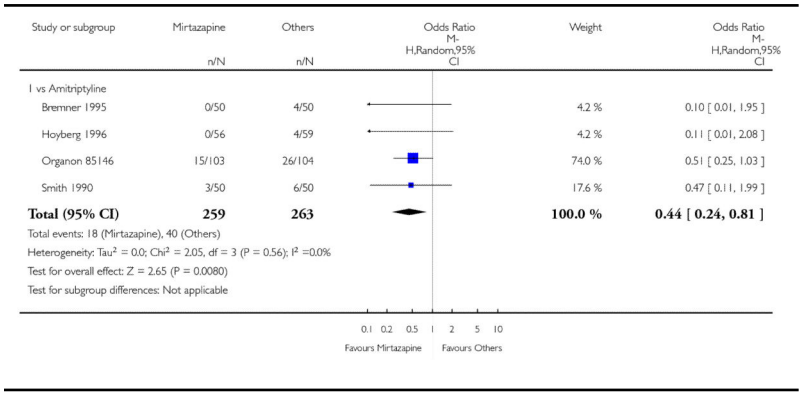
Analysis 1.11
Comparison 1 Mirtazapine versus TCAs, Outcome 11 Secondary outcome (having some adverse events)

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 11 Secondary outcome (having some adverse events)



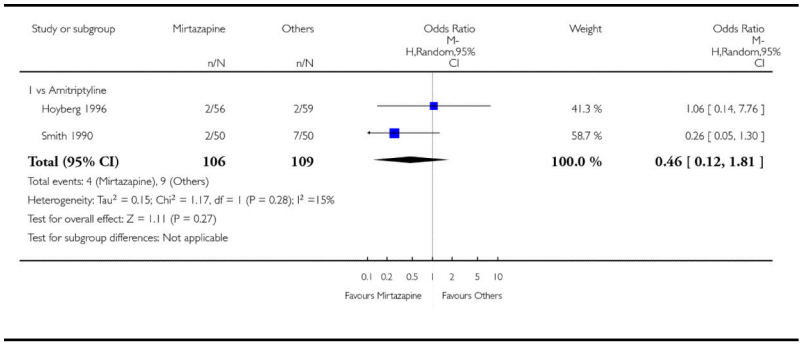
Analysis 1.12
Comparison 1 Mirtazapine versus TCAs, Outcome 12 Hypertension/Tachycardia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 12 Hypertension/Tachycardia



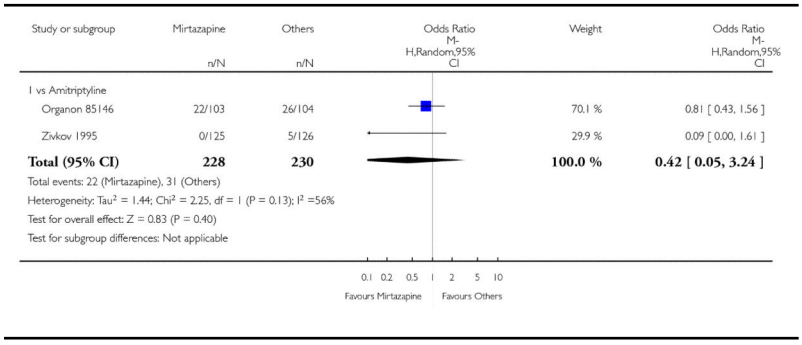
Analysis 1.13
Comparison 1 Mirtazapine versus TCAs, Outcome 13 Hypotension/Bradycardia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 13 Hypotension/Bradycardia



Analysis 1.14
Comparison 1 Mirtazapine versus TCAs, Outcome 14 Sweating

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 14 Sweating



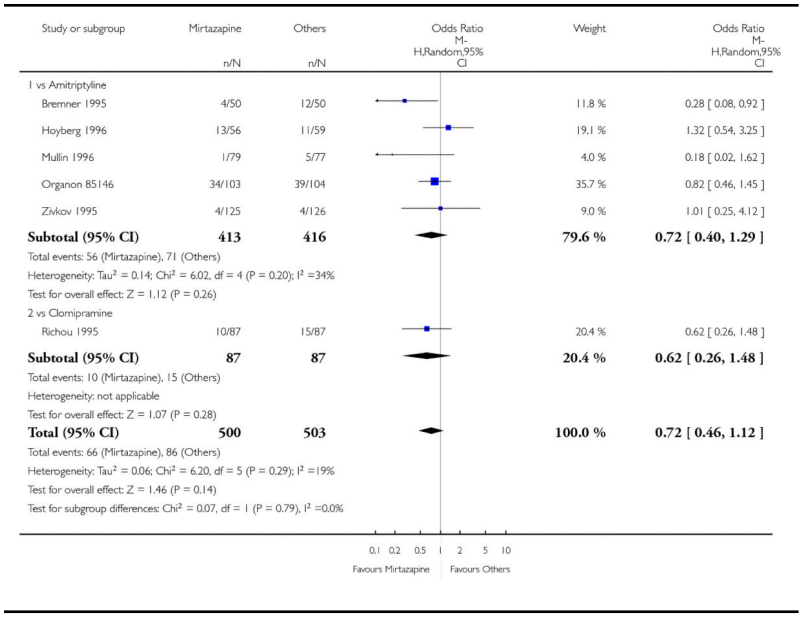
Analysis 1.15

Comparison 1 Mirtazapine versus TCAs, Outcome 15 Constipation

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 15 Constipation



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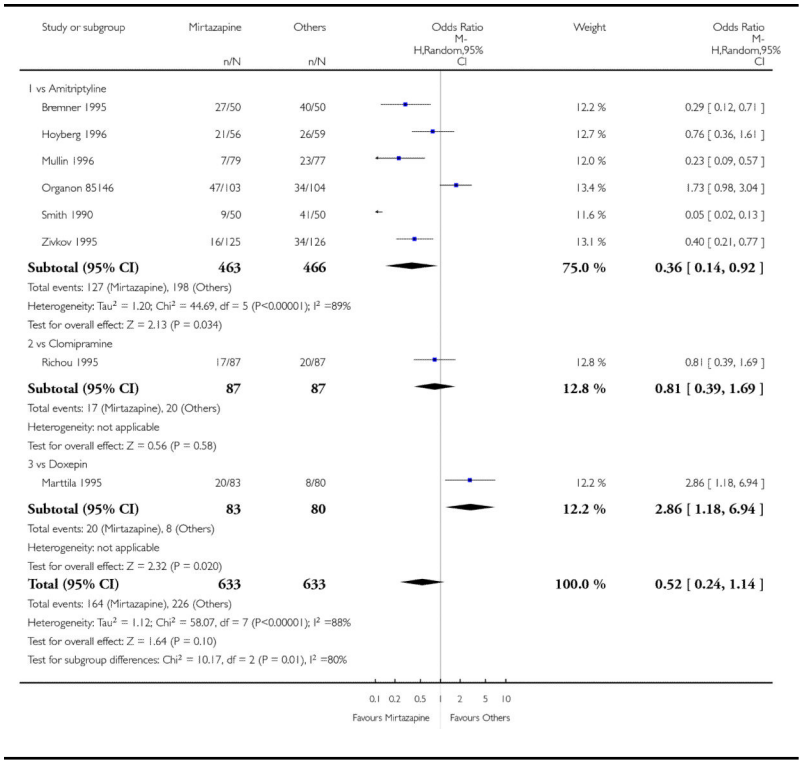
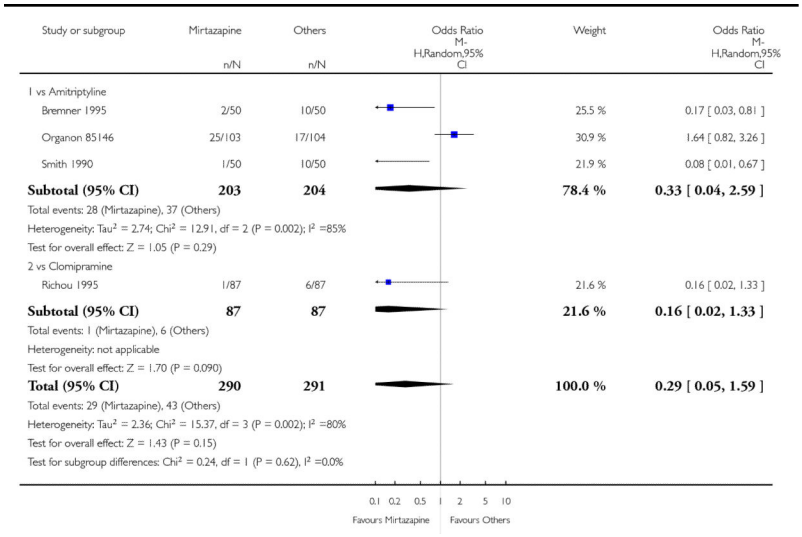
Analysis 1.16
Comparison 1 Mirtazapine versus TCAs, Outcome 16 Dry mouth/Decreased salivation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 16 Dry mouth/Decreased salivation



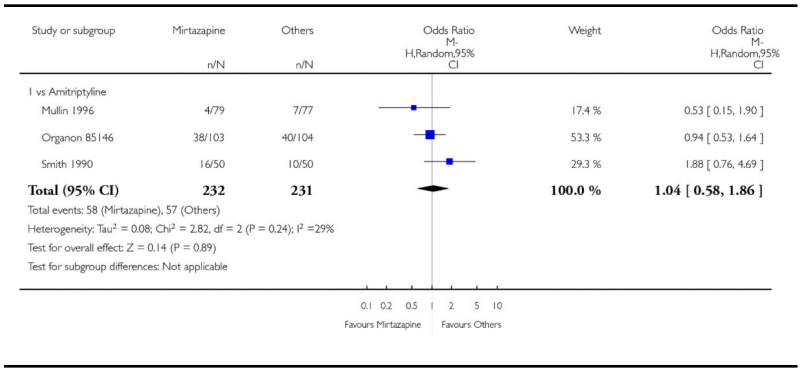
Analysis 1.17
Comparison 1 Mirtazapine versus TCAs, Outcome 17 Nausea/Vomiting/Gastric distress

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 17 Nausea/Vomiting/Gastric distress



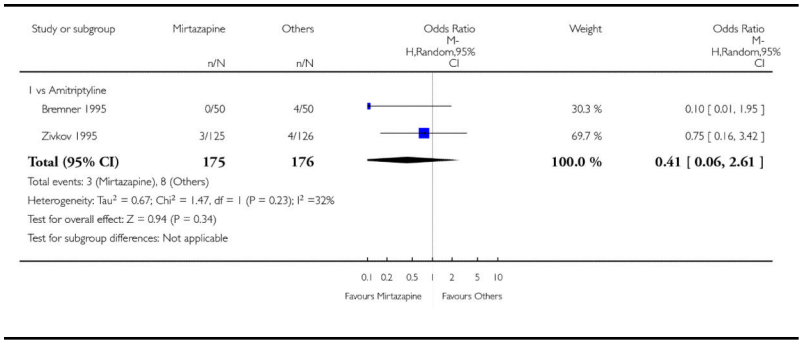
Analysis 1.18
Comparison 1 Mirtazapine versus TCAs, Outcome 18 Weight gain/Increased appetite

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 18 Weight gain/Increased appetite



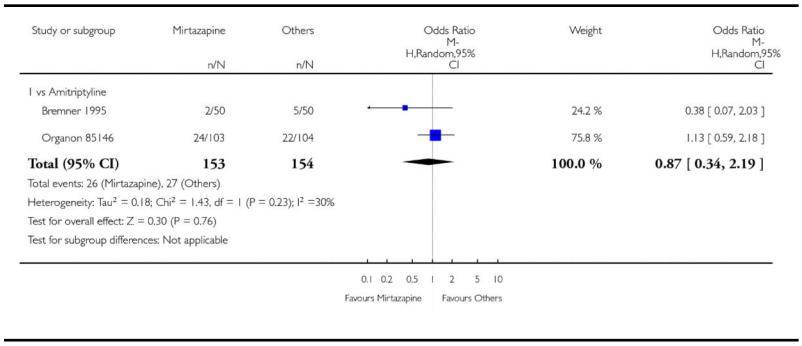
Analysis 1.19
Comparison 1 Mirtazapine versus TCAs, Outcome 19 Sexual dysfunction

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 19 Sexual dysfunction



Analysis 1.20
Comparison 1 Mirtazapine versus TCAs, Outcome 20 Anxiety/Agitation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 20 Anxiety/Agitation



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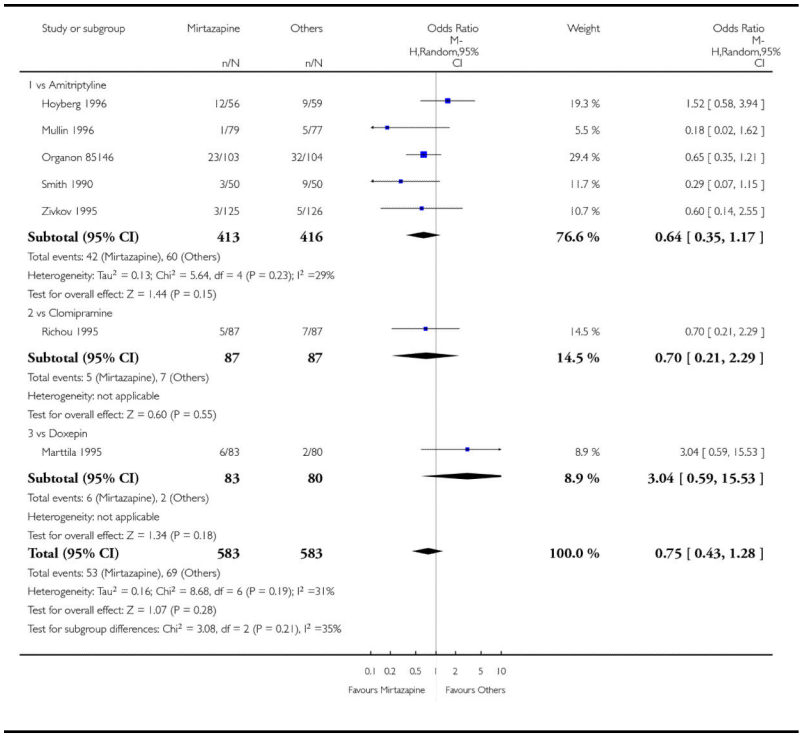
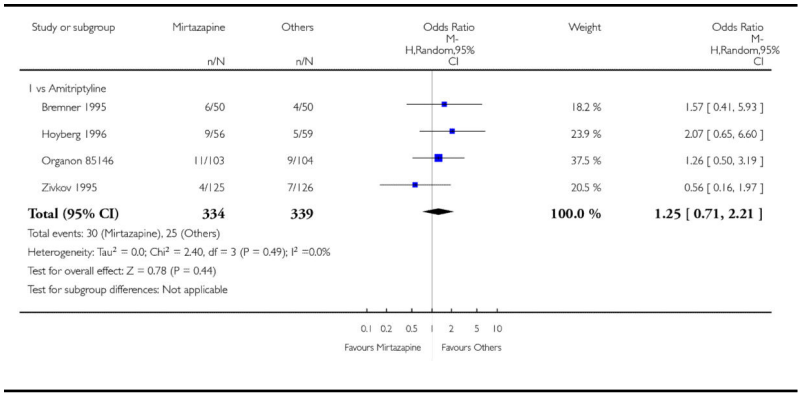
Analysis 1.21
Comparison 1 Mirtazapine versus TCAs, Outcome 21 Dizziness/Vertigo/Faintness

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 21 Dizziness/Vertigo/Faintness



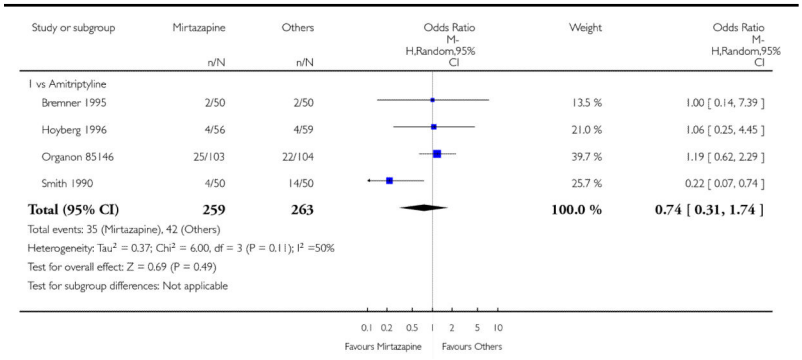
Analysis 1.22
Comparison 1 Mirtazapine versus TCAs, Outcome 22 Fatigue/Tiredness/Asthenia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 22 Fatigue/Tiredness/Asthenia



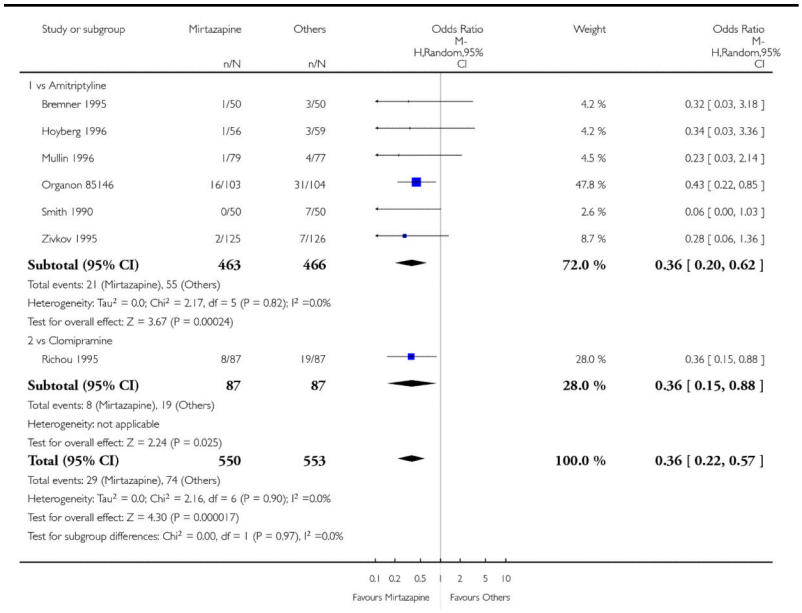
Analysis 1.23
Comparison 1 Mirtazapine versus TCAs, Outcome 23 Headache

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 23 Headache



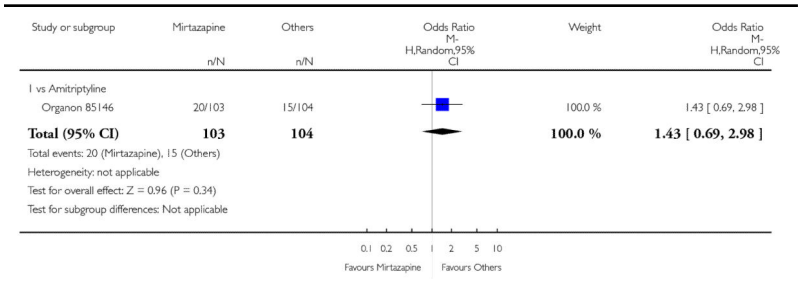
Analysis 1.24
Comparison 1 Mirtazapine versus TCAs, Outcome 24 Tremor

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 24 Tremor



Analysis 1.25
Comparison 1 Mirtazapine versus TCAs, Outcome 25 Sleep disturbance

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 1 Mirtazapine versus TCAs
Outcome: 25 Sleep disturbance



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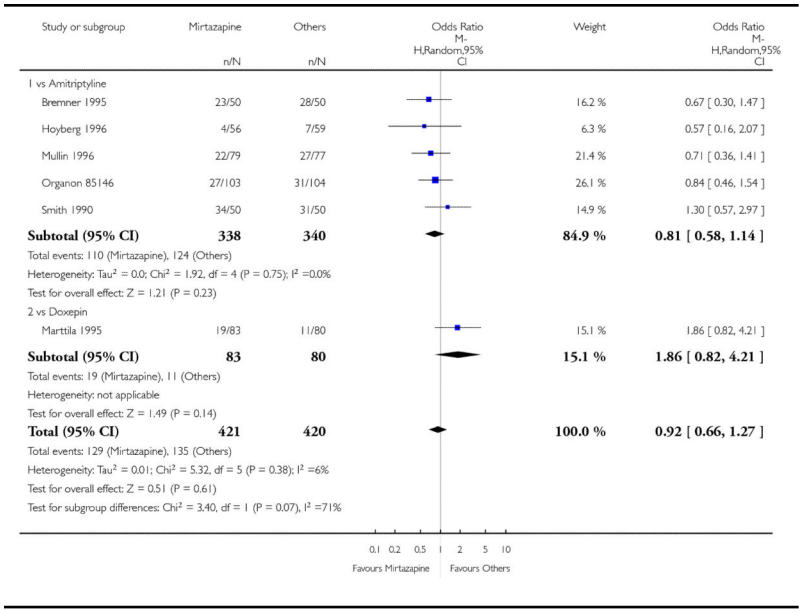
Analysis 1.26
Comparison 1 Mirtazapine versus TCAs, Outcome 26 Sleepiness/Drowsiness/Somnolence

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 26 Sleepiness/Drowsiness/Somnolence



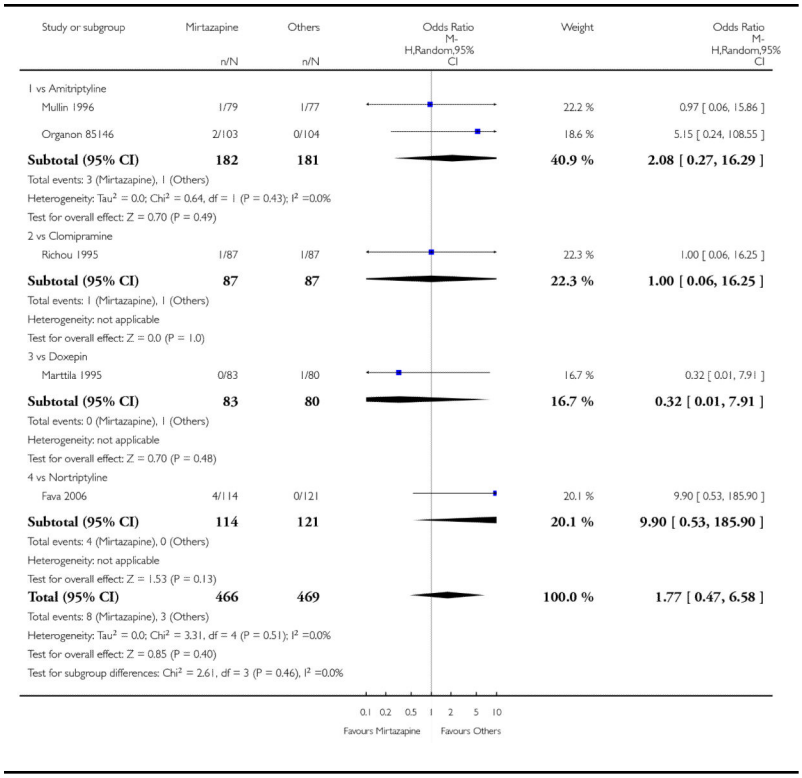
Analysis 1.27

Comparison 1 Mirtazapine versus TCAs, Outcome 27 Suicide attempt

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 27 Suicide attempt



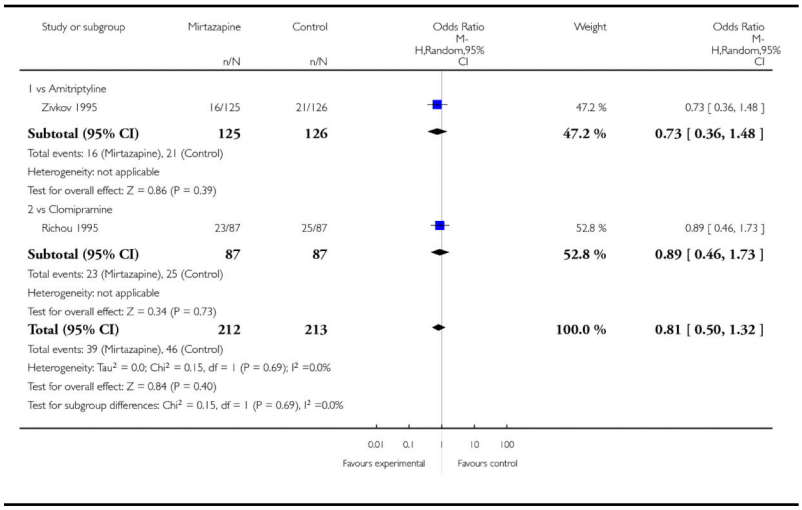
Analysis 1.28

Comparison 1 Mirtazapine versus TCAs, Outcome 28 Subgroup analysis: Response at 2 weeks: Treatment settings: Psychiatric inpatients

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 28 Subgroup analysis: Response at 2 weeks: Treatment settings: Psychiatric inpatients



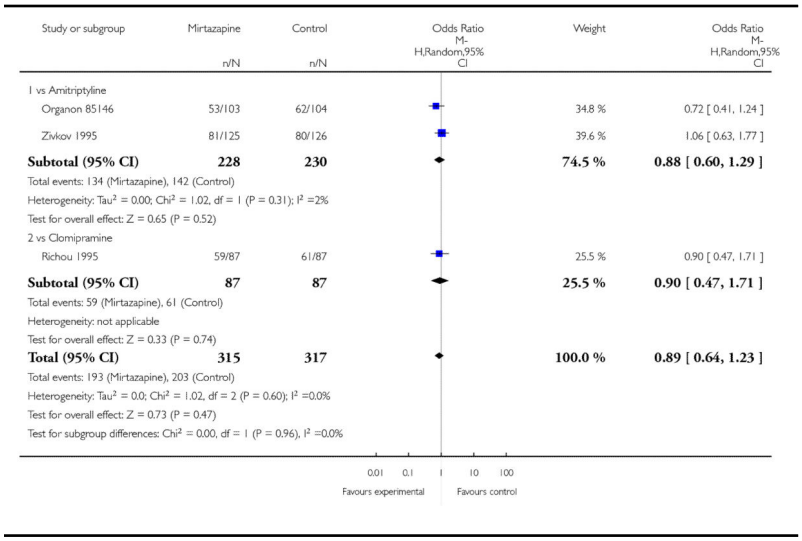
Analysis 1.29

Comparison 1 Mirtazapine versus TCAs, Outcome 29 Subgroup analysis: Response at end of the acute-phase treatment: Treatment settings: Psychiatric inpatients

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 29 Subgroup analysis: Response at end of the acute-phase treatment: Treatment settings: Psychiatric inpatients



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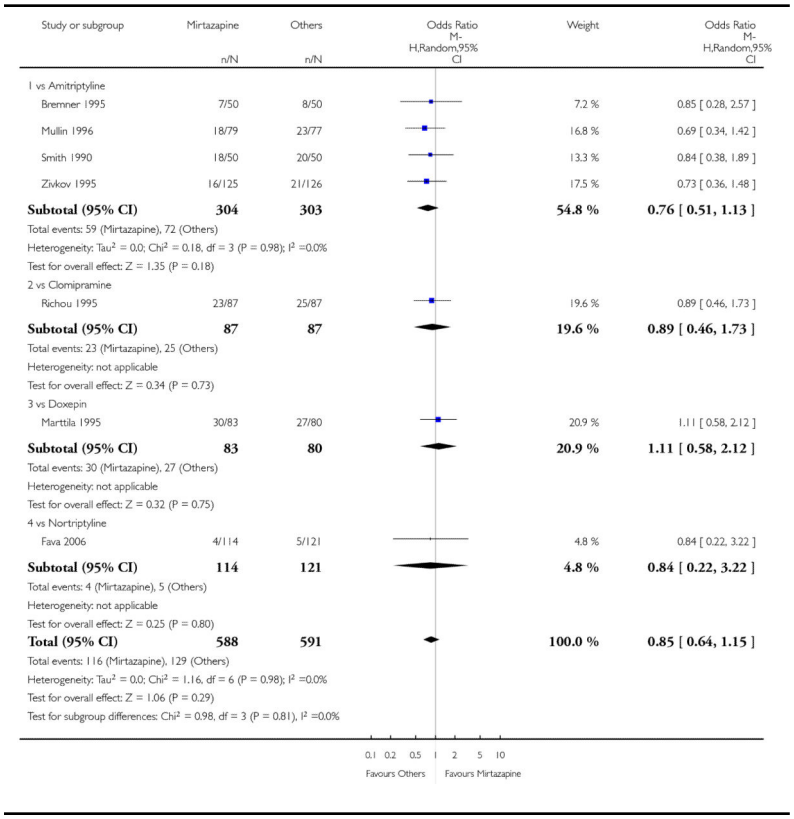
Analysis 1.30

Comparison 1 Mirtazapine versus TCAs, Outcome 30 Sensitivity analysis: Response at 2 weeks: Studies without imputation

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 30 Sensitivity analysis: Response at 2 weeks: Studies without imputation



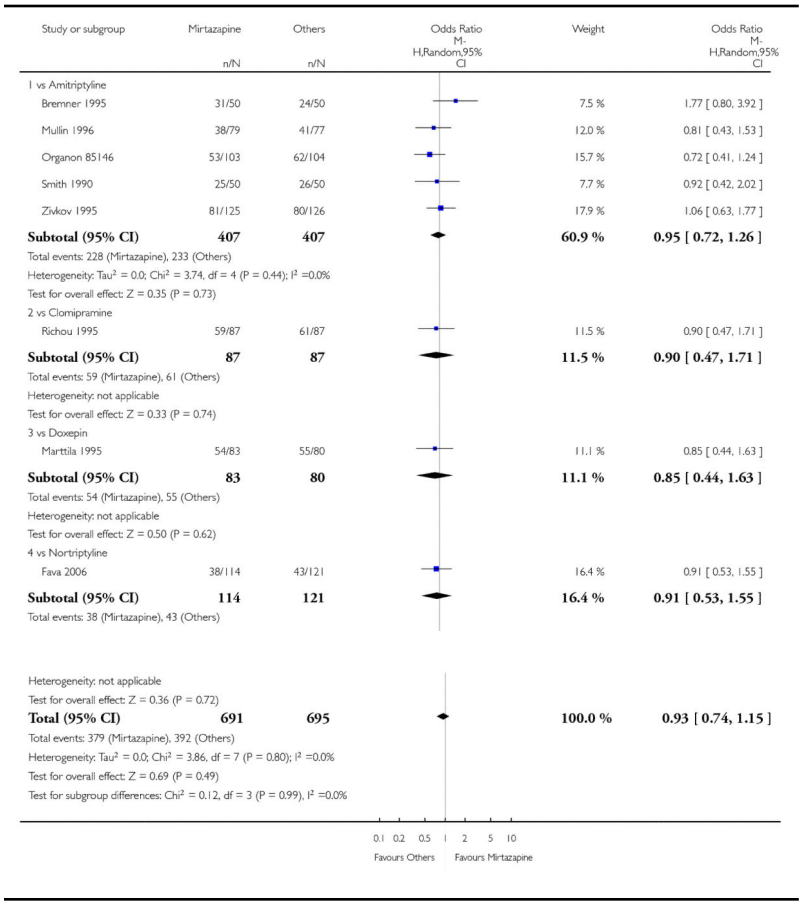
Analysis 1.31

Comparison 1 Mirtazapine versus TCAs, Outcome 31 Sensitivity analysis: Response at end of the acute-phase treatment: Studies without imputation

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 1 Mirtazapine versus TCAs

Outcome: 31 Sensitivity analysis: Response at end of the acute-phase treatment: Studies without imputation



Analysis 1.32

Comparison 1 Mirtazapine versus TCAs, Outcome 32 Secondary outcome (SKEWED DATA: depression severity) at 2 weeks

Secondary outcome (SKEWED DATA: depression severity) at 2 weeks

Study	Comparator drug	Measurement	Mirtazapine: mean	SD	N	Comparator: mean	SD	N	note
Hoyberg 1996	Amitripty-line	HAMD-21 change score	−4.7	4.5	54	−5.2	4.4	59	

Analysis 1.33

Comparison 1 Mirtazapine versus TCAs, Outcome 33 Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment

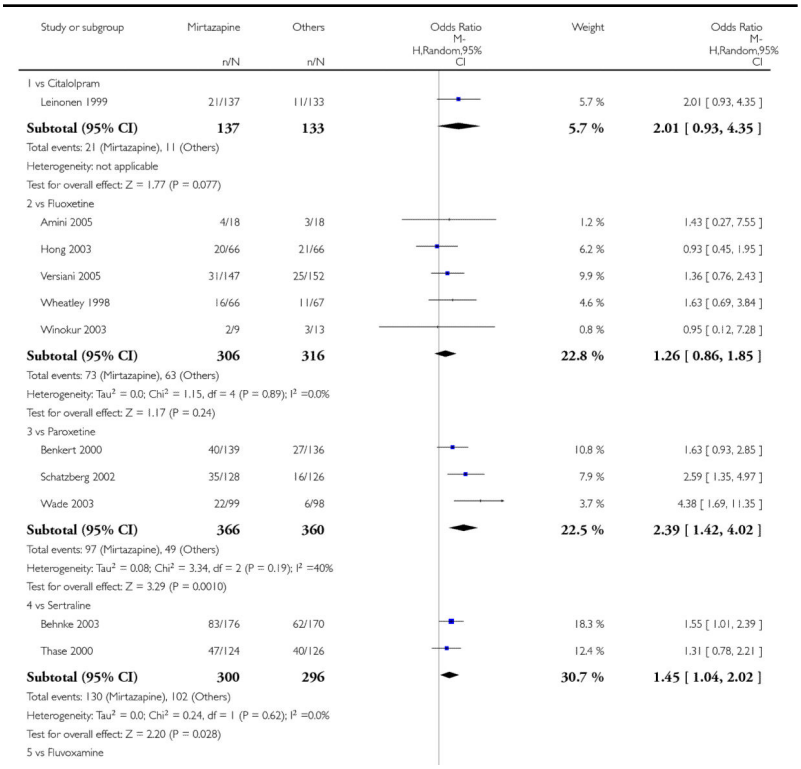
Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment

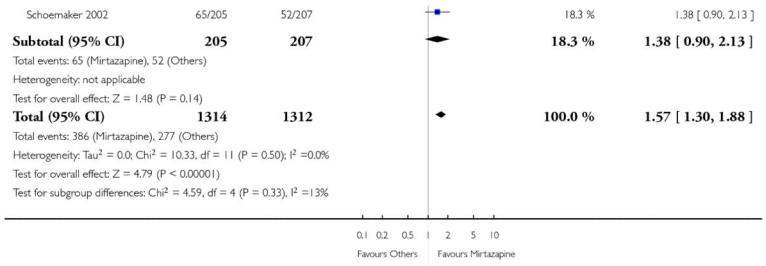
Study	Comparator	Measurement	Mirtazapine: mean	SD	N	Comparator: mean	SD	N	Note
Hoyberg 1996	Amitripty-line	HAMD-21 change score	−11.1	7.9	54	−13.1	7.5	59	
Marttila 1995	Doxepin	HAMD-17	9.15	7.5	83	9.0	6.35	80	
Mullin 1996	Amitripty-line	HAMD-17	11.7	7.3	71	10.7	6.8	71	
Zivkov 1995	Amitripty-line	HAMD-21	12.8	10.1	113	12.0	10.0	111	

Analysis 2.1

Comparison 2 Mirtazapine versus SSRIs, Outcome 1 Primary outcome (response) at 2 weeks

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 1 Primary outcome (response) at 2 weeks





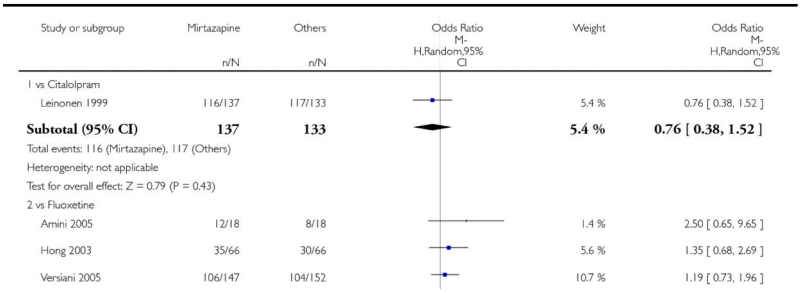
Analysis 2.2

Comparison 2 Mirtazapine versus SSRIs, Outcome 2 Primary outcome (response) at end of the acute-phase treatment

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 2 Primary outcome (response) at end of the acute-phase treatment



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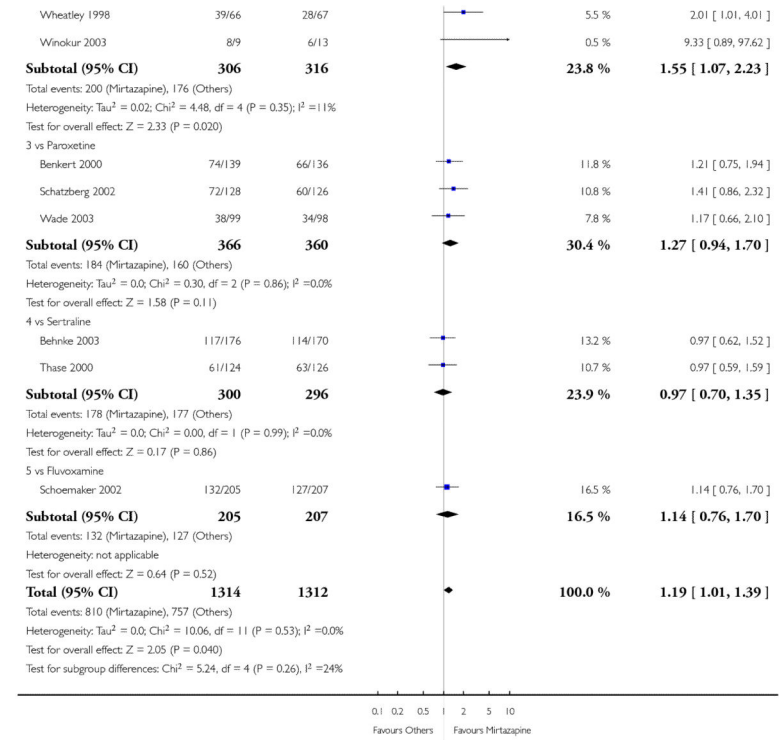


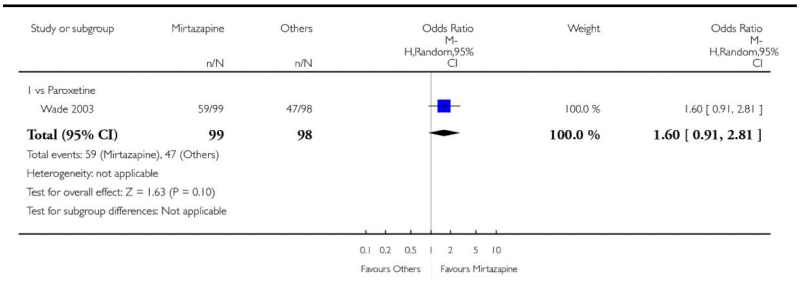
Analysis 2.3

Comparison 2 Mirtazapine versus SSRIs, Outcome 3 Primary outcome (response) at end of the continuation treatment

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 3 Primary outcome (response) at end of the continuation treatment



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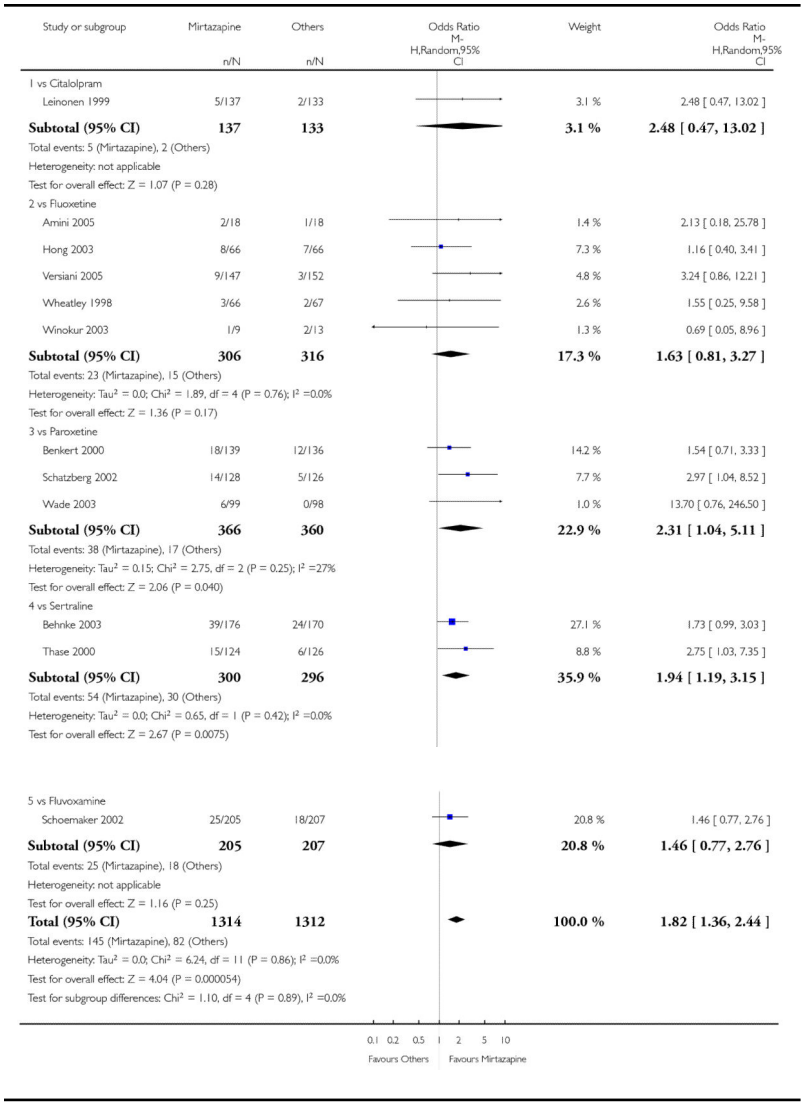
Analysis 2.4
Comparison 2 Mirtazapine versus SSRIs, Outcome 4 Secondary outcome (remission) at 2 weeks

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 4 Secondary outcome (remission) at 2 weeks



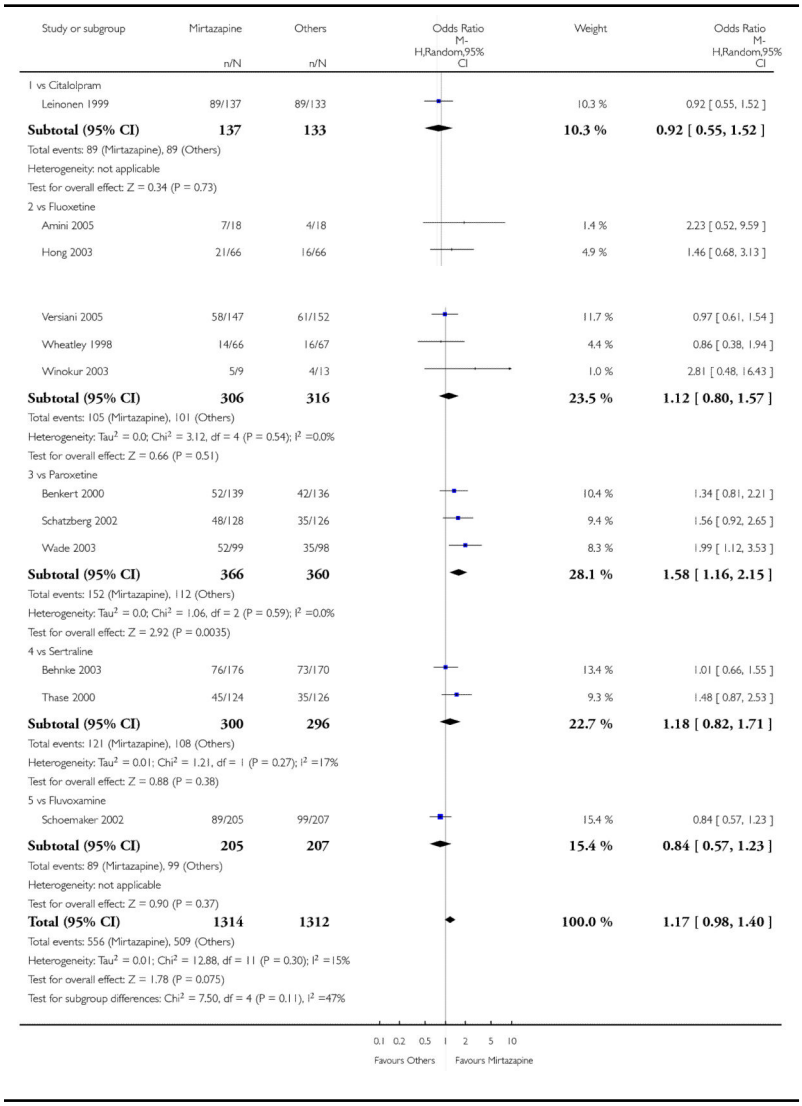
Analysis 2.5

Comparison 2 Mirtazapine versus SSRIs, Outcome 5 Secondary outcome (remission) at end of the acute-phase treatment

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 5 Secondary outcome (remission) at end of the acute-phase treatment



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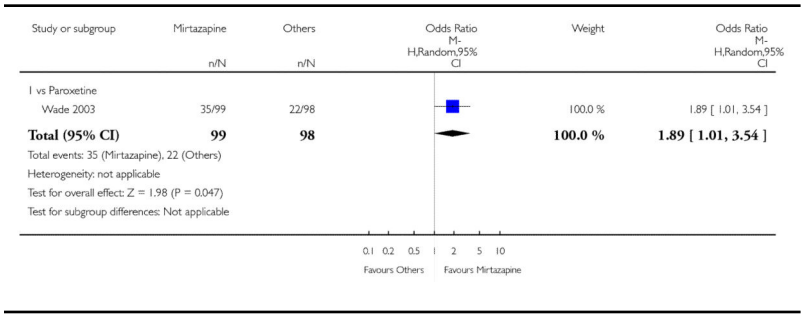
Analysis 2.6

Comparison 2 Mirtazapine versus SSRIs, Outcome 6 Secondary outcome (remission) at end of the continuation treatment

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 6 Secondary outcome (remission) at end of the continuation treatment



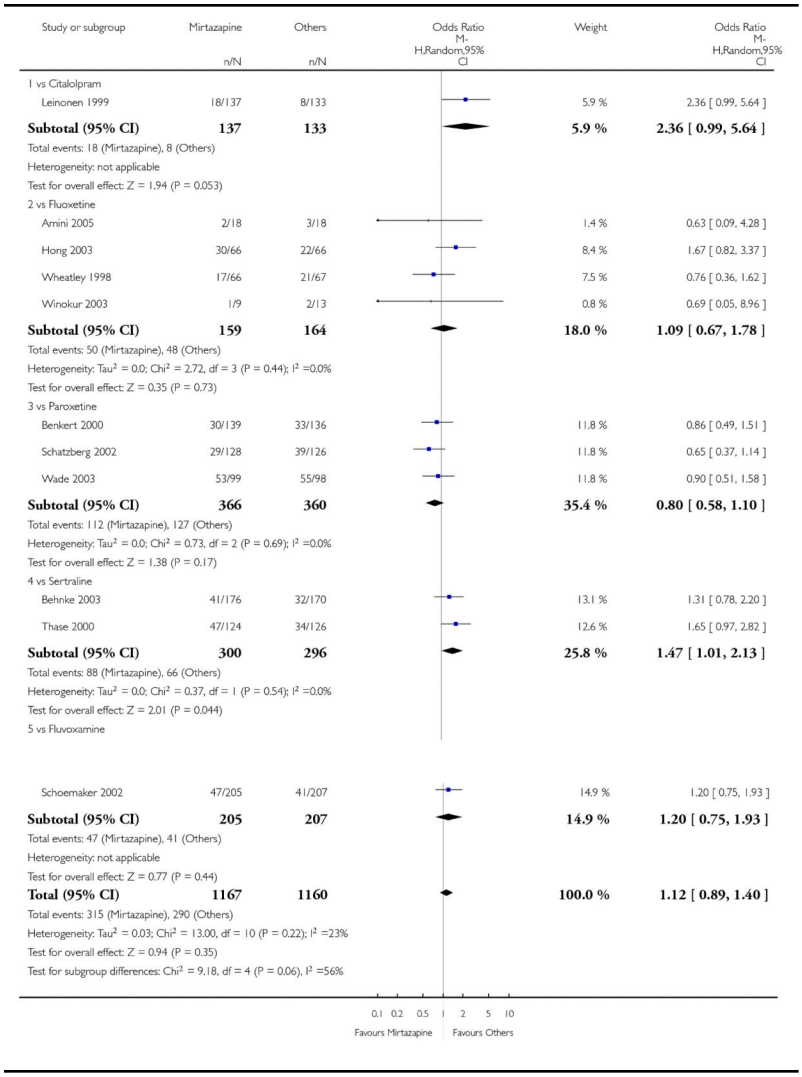
Analysis 2.7

Comparison 2 Mirtazapine versus SSRIs, Outcome 7 Secondary outcome (withdrawal due to any reason)

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 7 Secondary outcome (withdrawal due to any reason)



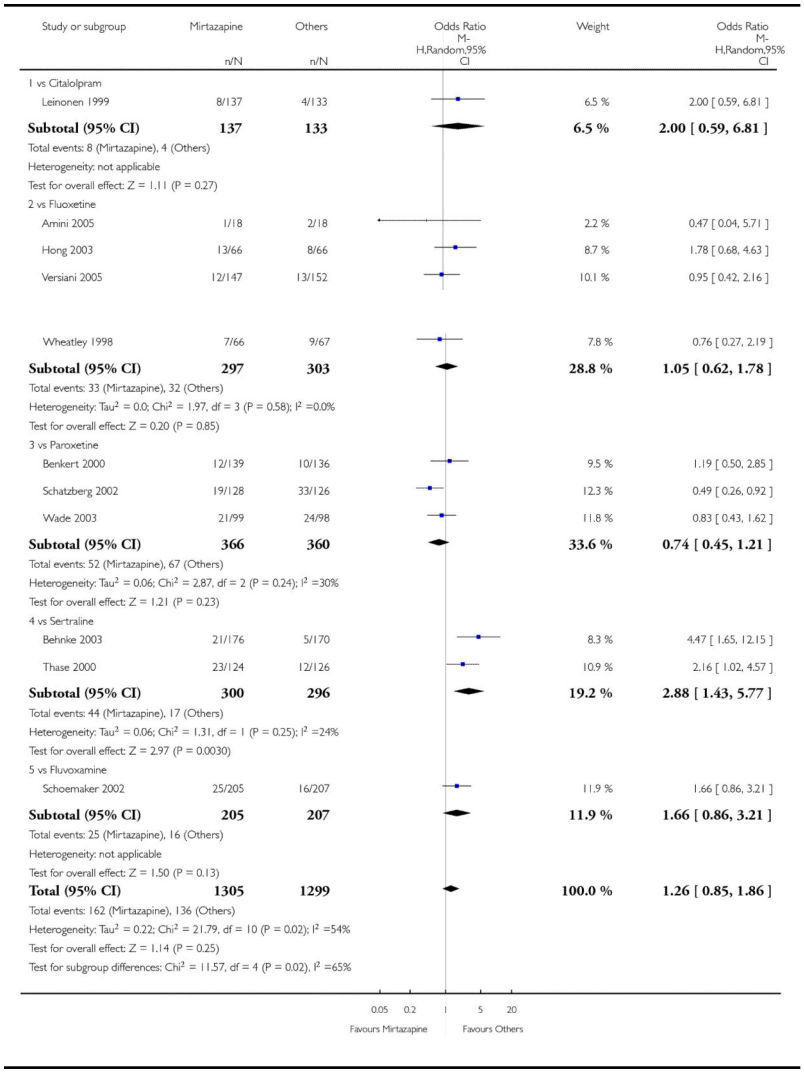
Analysis 2.8

Comparison 2 Mirtazapine versus SSRIs, Outcome 8 Secondary outcome (withdrawal due to adverse events)

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 8 Secondary outcome (withdrawal due to adverse events)



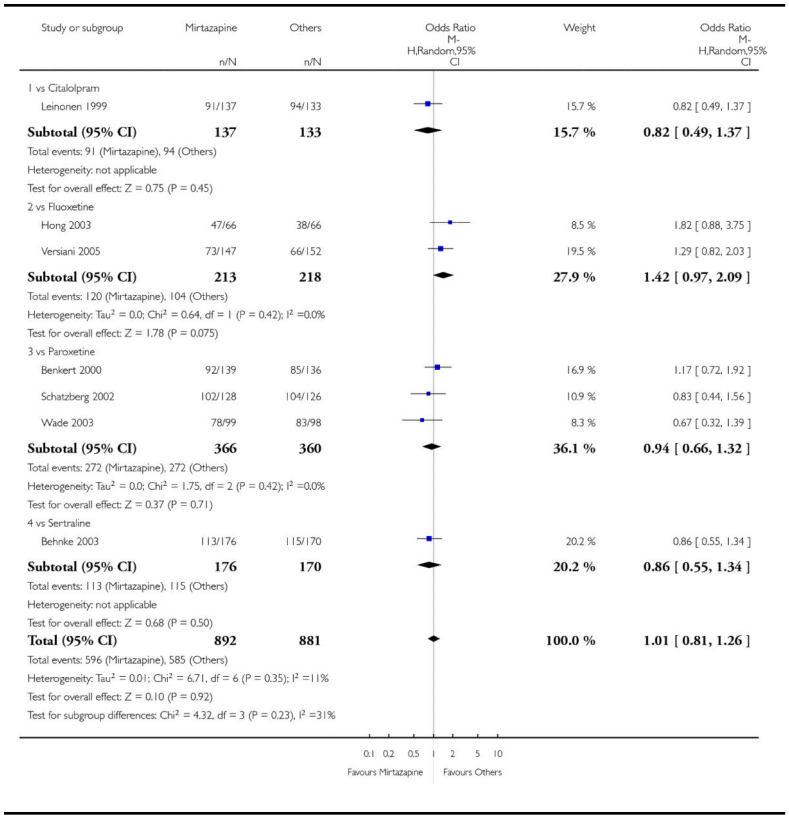
Analysis 2.9

Comparison 2 Mirtazapine versus SSRIs, Outcome 9 Secondary outcome (having some adverse events)

Review: Mirtazapine versus other antidepressive agents for depression

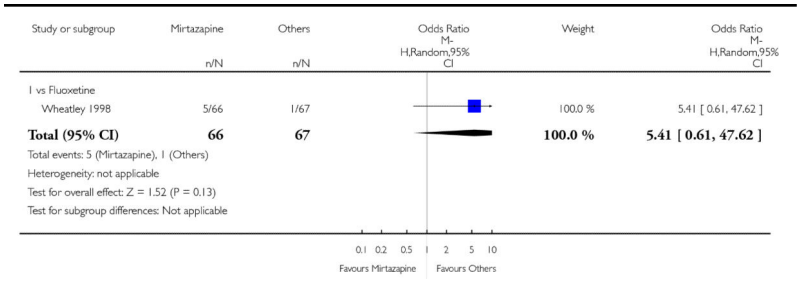
Comparison: 2 Mirtazapine versus SSRIs

Outcome: 9 Secondary outcome (having some adverse events)



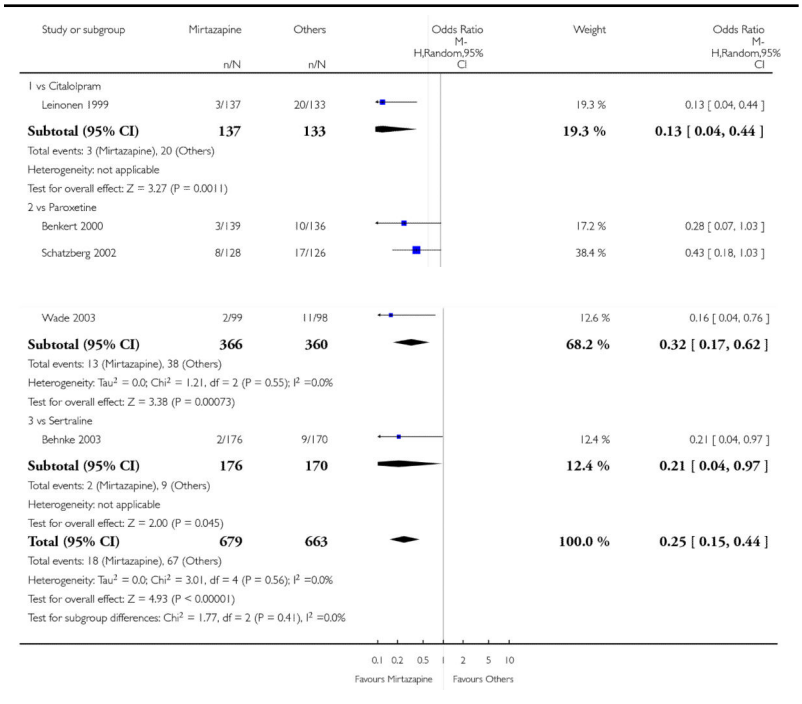
Analysis 2.10
Comparison 2 Mirtazapine versus SSRIs, Outcome 10 Hypotension/Bradycardia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 10 Hypotension/Bradycardia



Analysis 2.11
Comparison 2 Mirtazapine versus SSRIs, Outcome 11 Sweating

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 11 Sweating



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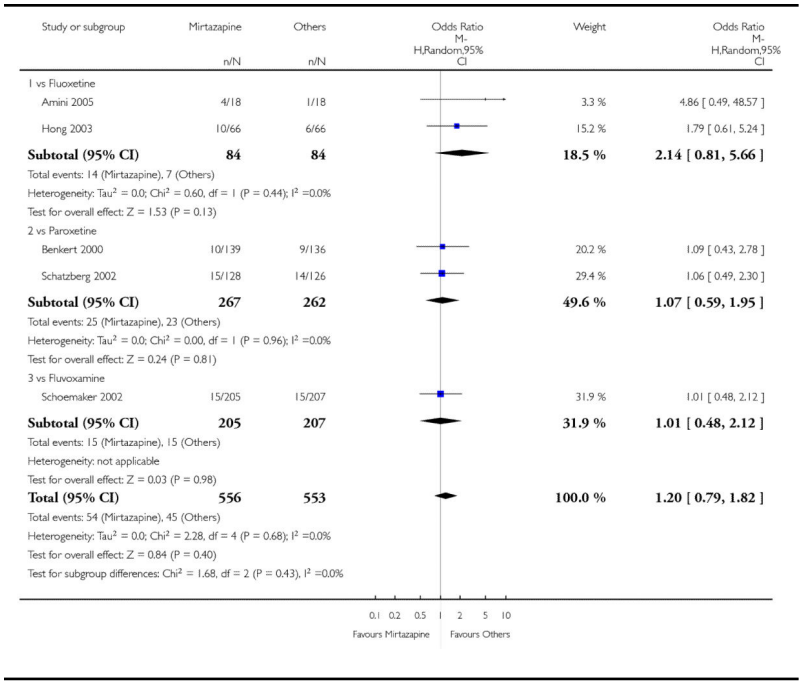
Analysis 2.12

Comparison 2 Mirtazapine versus SSRIs, Outcome 12 Constipation

Review: Mirtazapine versus other antidepressive agents for depression

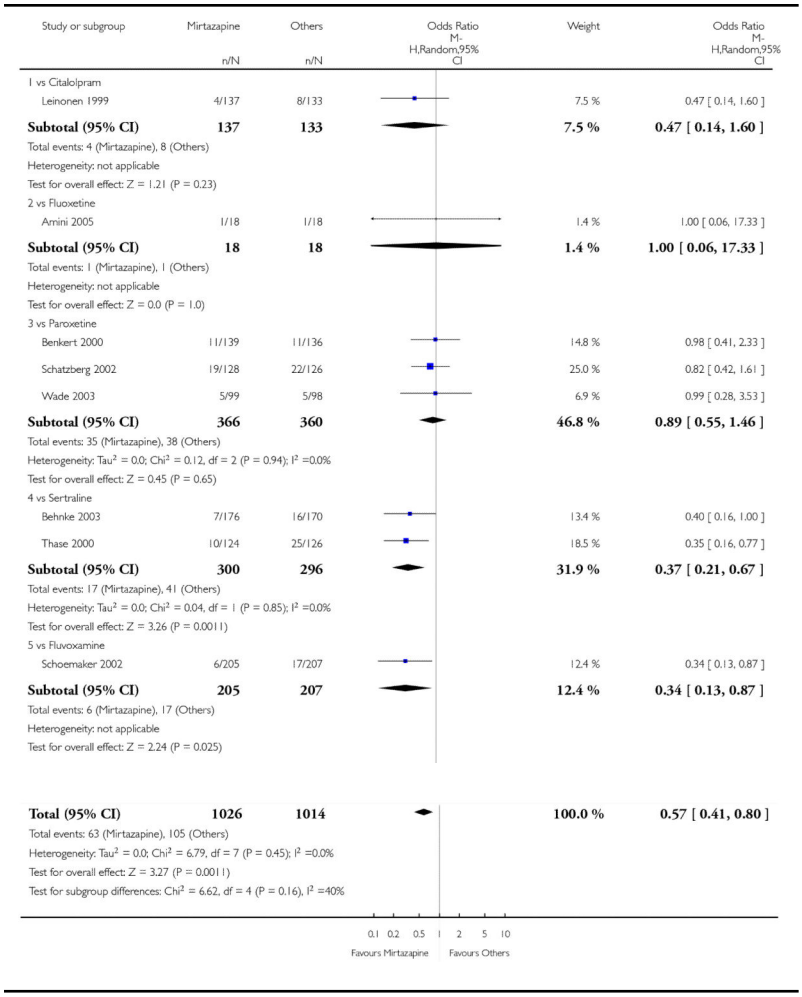
Comparison: 2 Mirtazapine versus SSRIs

Outcome: 12 Constipation



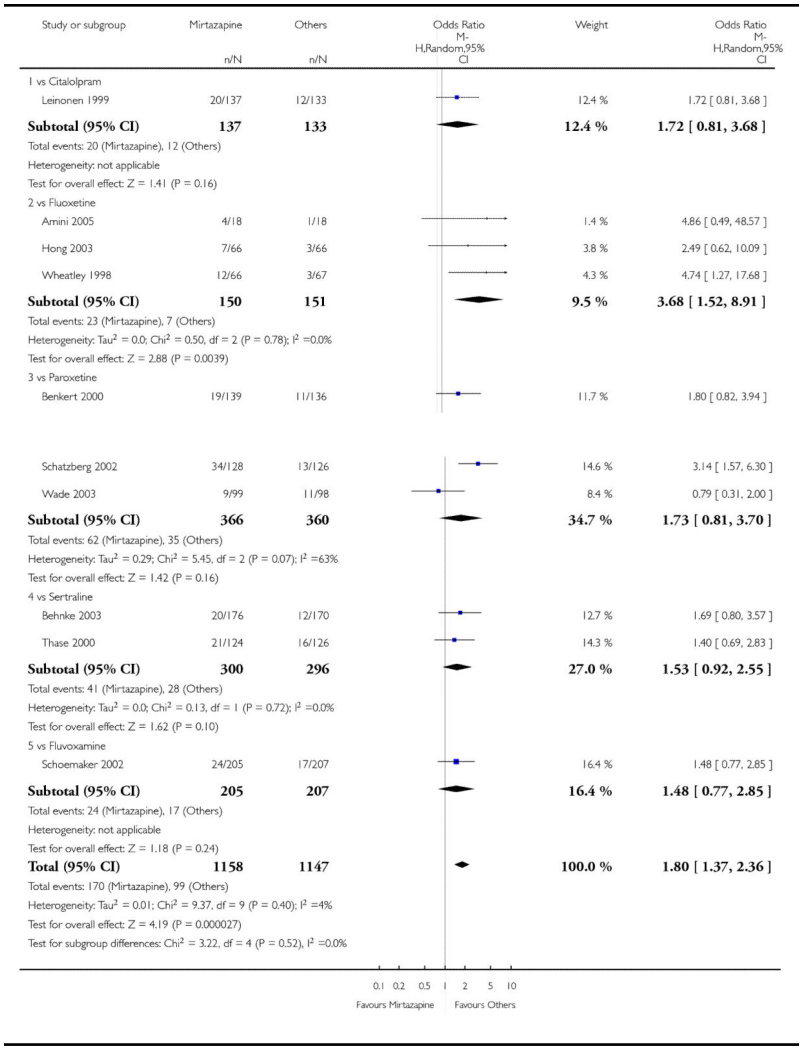
Analysis 2.13
Comparison 2 Mirtazapine versus SSRIs, Outcome 13 Diarrhoea

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 13 Diarrhoea



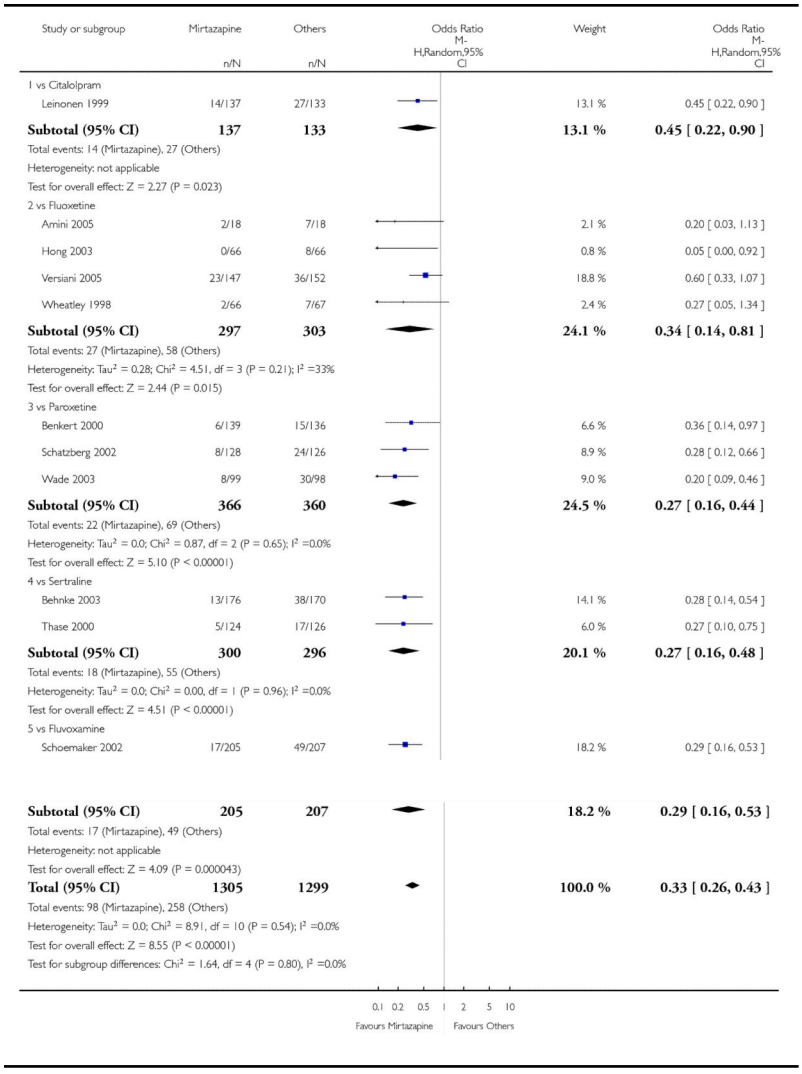
Analysis 2.14
Comparison 2 Mirtazapine versus SSRIs, Outcome 14 Dry mouth/Decreased salivation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 14 Dry mouth/Decreased salivation



Analysis 2.15
Comparison 2 Mirtazapine versus SSRIs, Outcome 15 Nausea/Vomiting/Gastric distress

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 15 Nausea/Vomiting/Gastric distress



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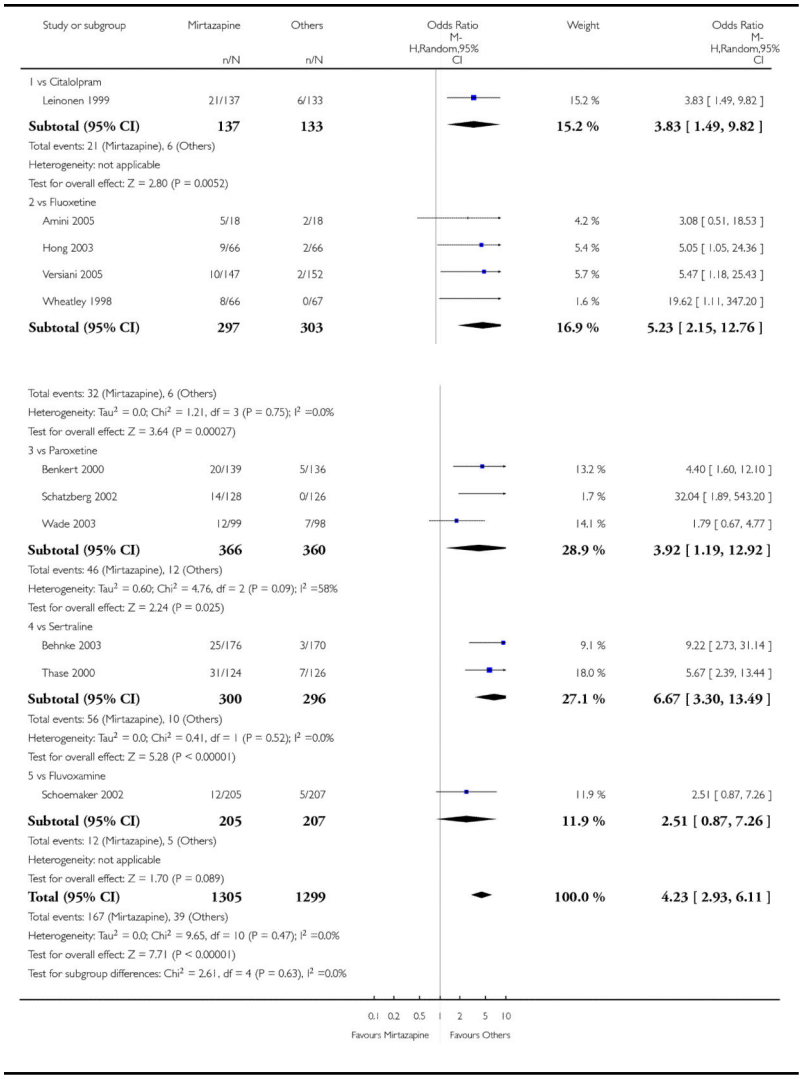
Analysis 2.16
Comparison 2 Mirtazapine versus SSRIs, Outcome 16 Weight gain/Increased appetite

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 16 Weight gain/Increased appetite



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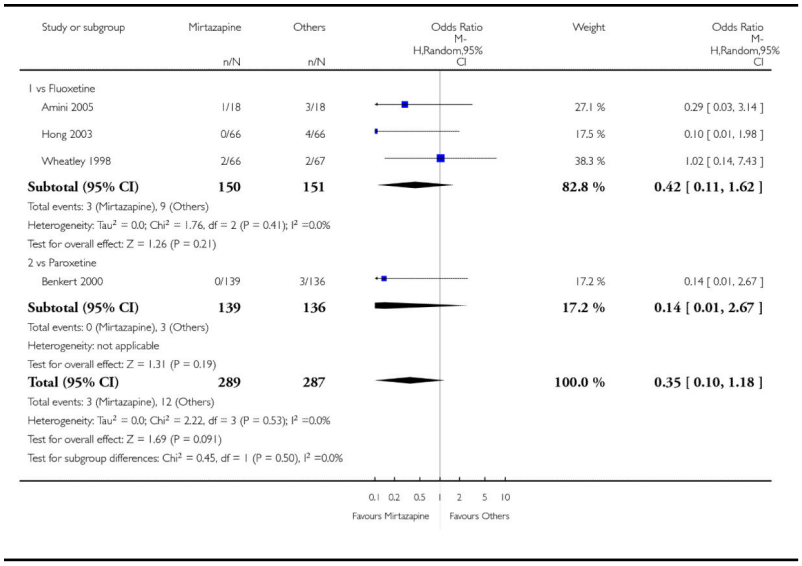
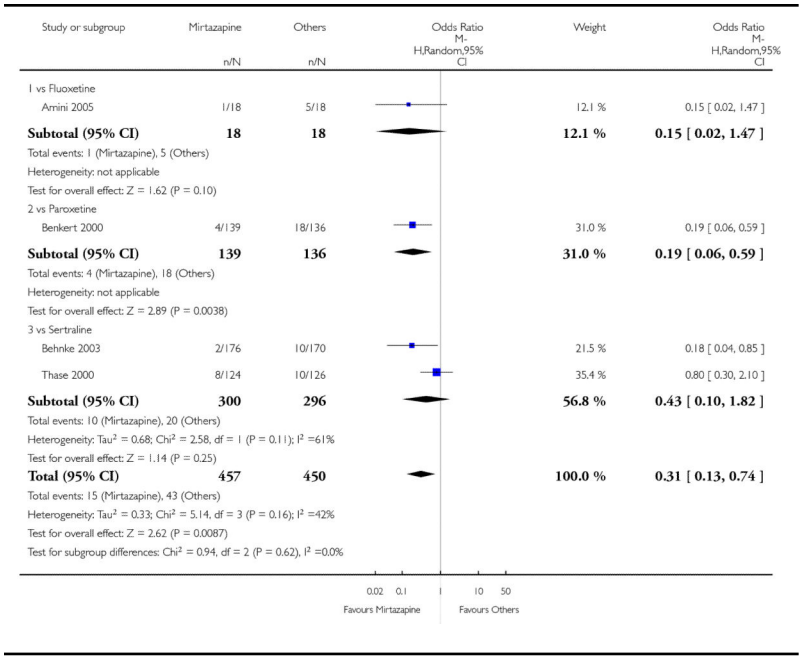
Analysis 2.17
Comparison 2 Mirtazapine versus SSRIs, Outcome 17 Weight loss/Anorexia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 17 Weight loss/Anorexia



Analysis 2.18
Comparison 2 Mirtazapine versus SSRIs, Outcome 18 Sexual dysfunction

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 18 Sexual dysfunction



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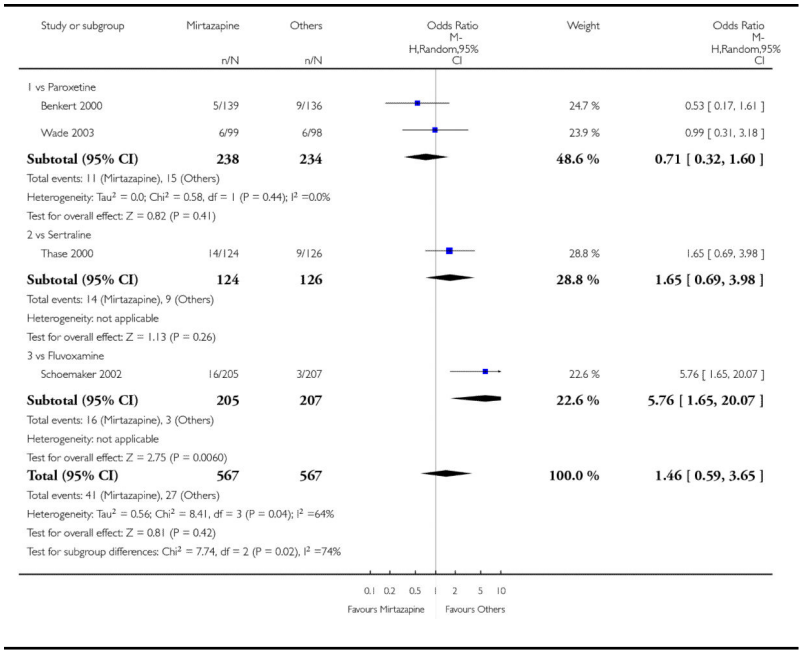
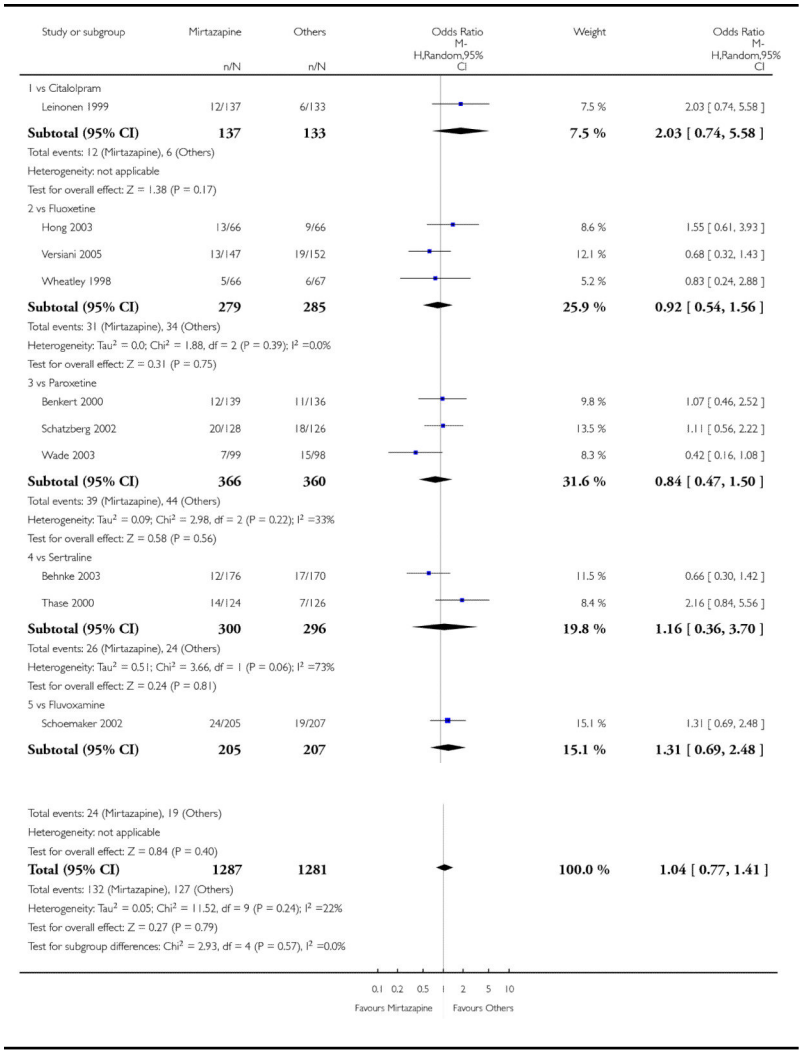
Analysis 2.19
Comparison 2 Mirtazapine versus SSRIs, Outcome 19 Anxiety/Agitation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 19 Anxiety/Agitation



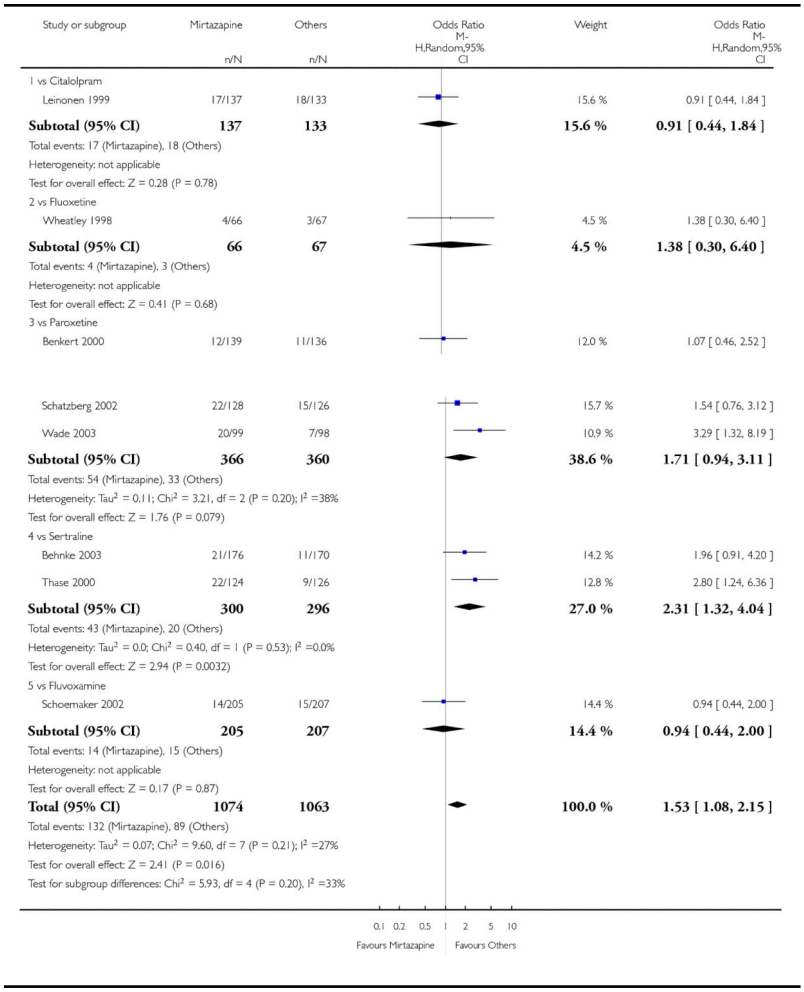
Analysis 2.20
Comparison 2 Mirtazapine versus SSRIs, Outcome 20 Dizziness/Vertigo/Faintness

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 20 Dizziness/Vertigo/Faintness



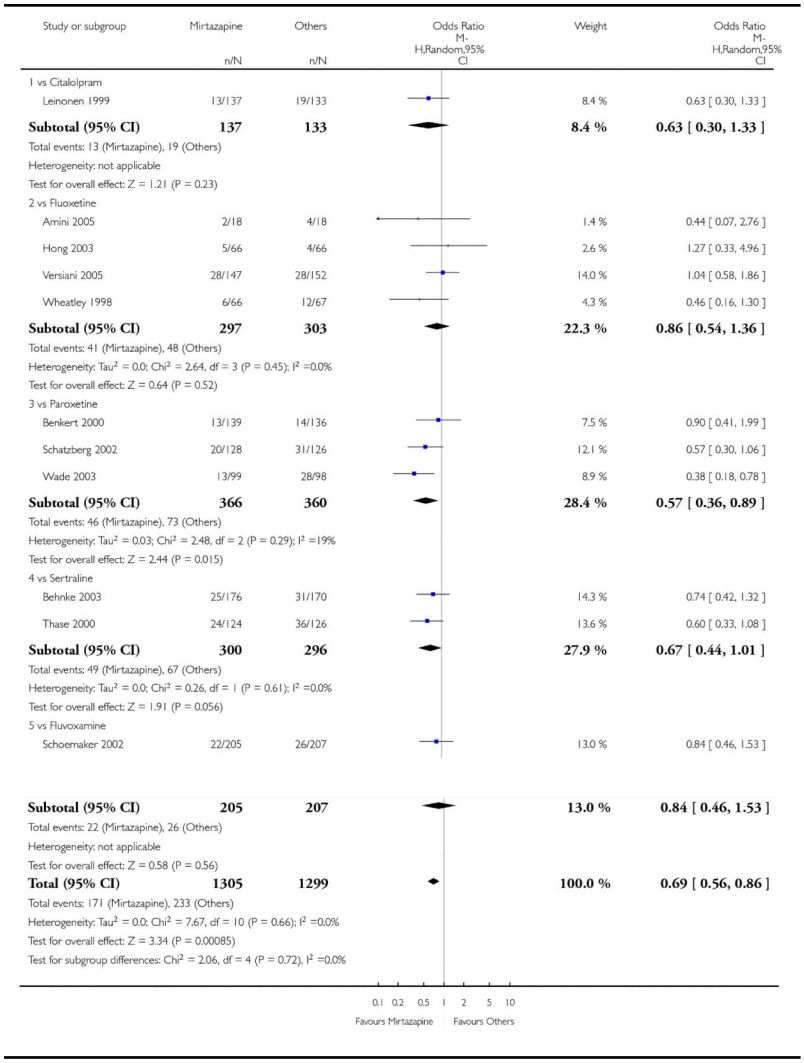
Analysis 2.21
Comparison 2 Mirtazapine versus SSRIs, Outcome 21 Fatigue/Tiredness/Asthenia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 21 Fatigue/Tiredness/Asthenia



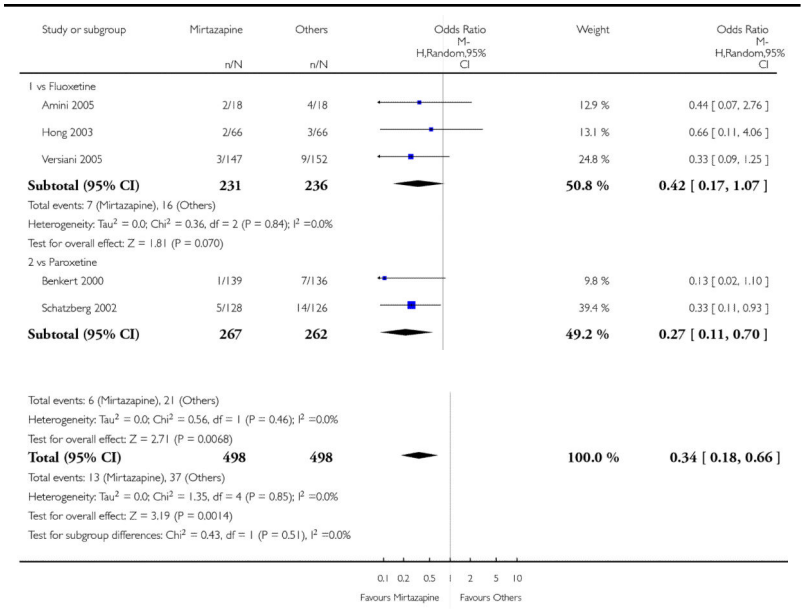
Analysis 2.22
Comparison 2 Mirtazapine versus SSRIs, Outcome 22 Headache

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 22 Headache



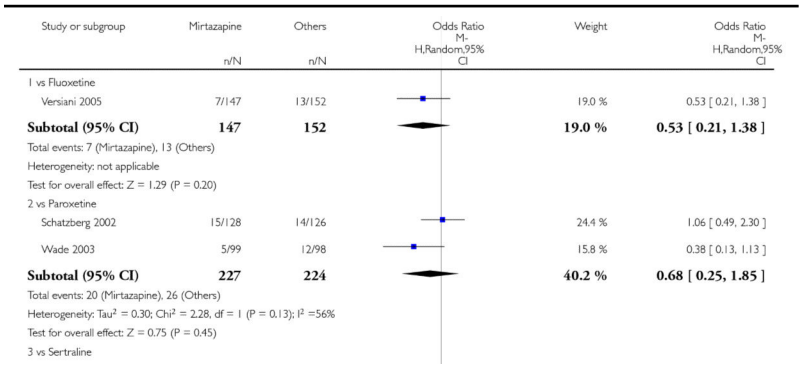
Analysis 2.23
Comparison 2 Mirtazapine versus SSRIs, Outcome 23 Tremor

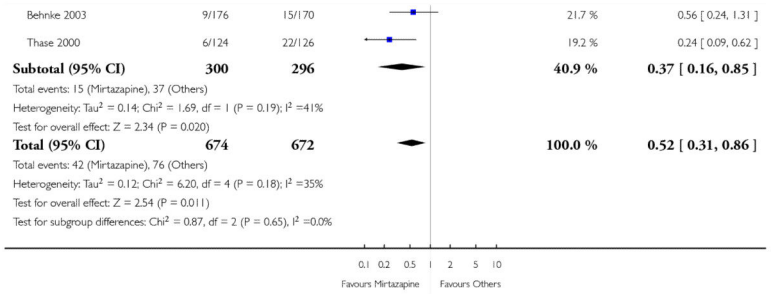
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 23 Tremor



Analysis 2.24
Comparison 2 Mirtazapine versus SSRIs, Outcome 24 Sleep disturbance

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 24 Sleep disturbance





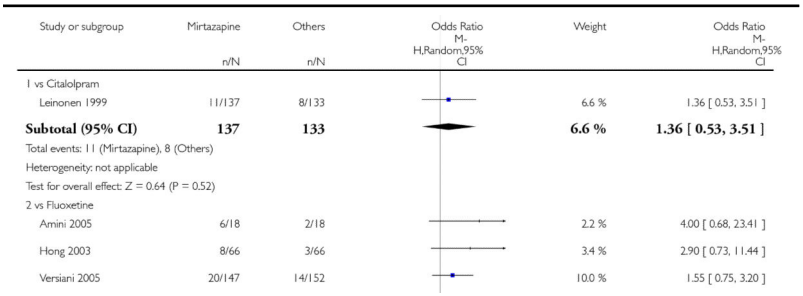
Analysis 2.25

Comparison 2 Mirtazapine versus SSRIs, Outcome 25 Sleepiness/Drowsiness/Somnolence

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 25 Sleepiness/Drowsiness/Somnolence



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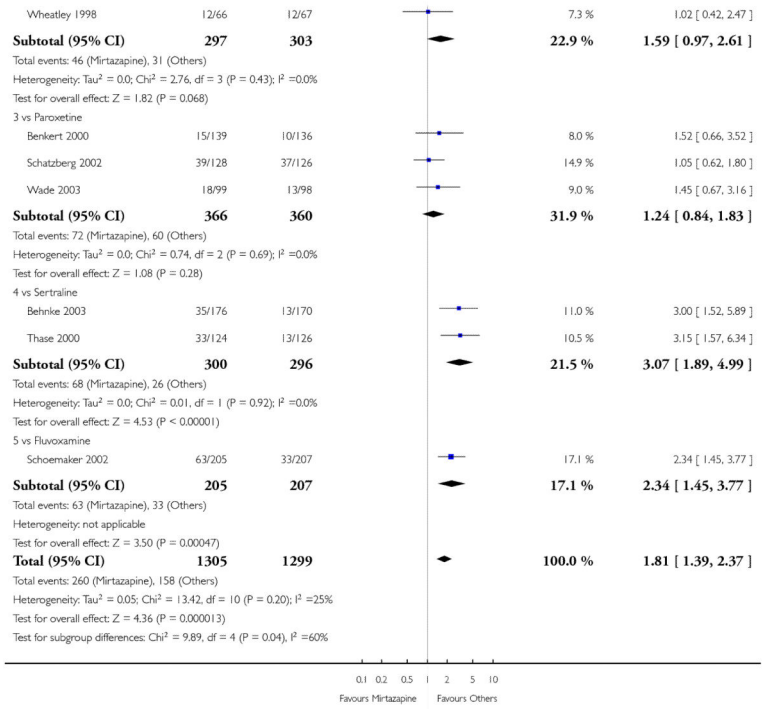


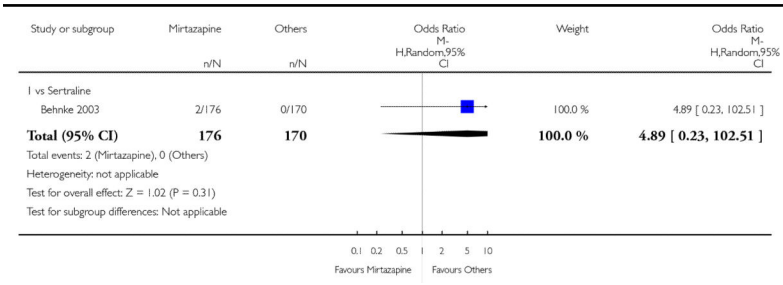
Analysis 2.26

Comparison 2 Mirtazapine versus SSRIs, Outcome 26 Suicide attempt

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 26 Suicide attempt



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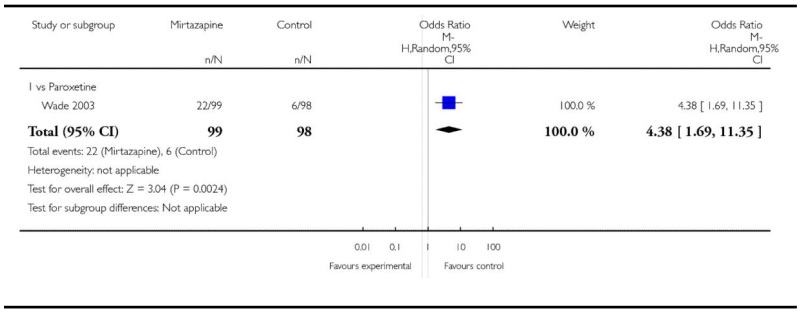
Analysis 2.27

Comparison 2 Mirtazapine versus SSRIs, Outcome 27 Subgroup analysis: Response at 2 weeks: Treatment settings: Outpatients in primary care

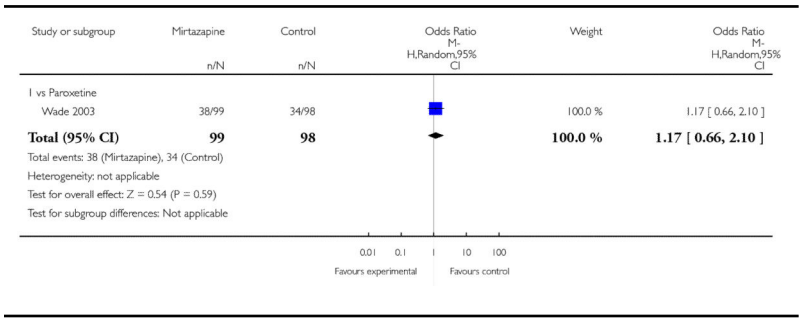
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 27 Subgroup analysis: Response at 2 weeks: Treatment settings: Outpatients in primary care



Analysis 2.28

Comparison 2 Mirtazapine versus SSRIs, Outcome 28 Subgroup analysis: Response at end of the acute-phase treatment: Treatment settings: Outpatients in primary care

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 2 Mirtazapine versus SSRIs
Outcome: 28 Subgroup analysis: Response at end of the acute-phase treatment: Treatment settings: Outpatients in primary care



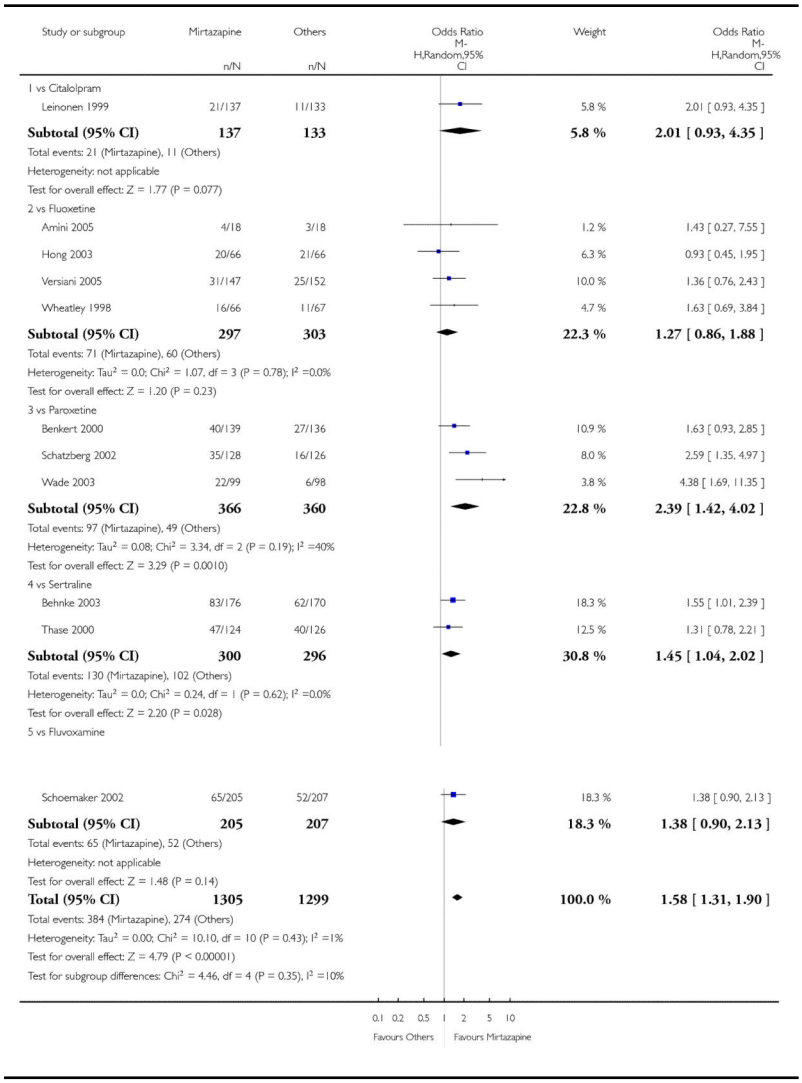
Analysis 2.29

Comparison 2 Mirtazapine versus SSRIs, Outcome 29 Sensitivity analysis: Response at 2 weeks: Studies without imputation

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 29 Sensitivity analysis: Response at 2 weeks: Studies without imputation



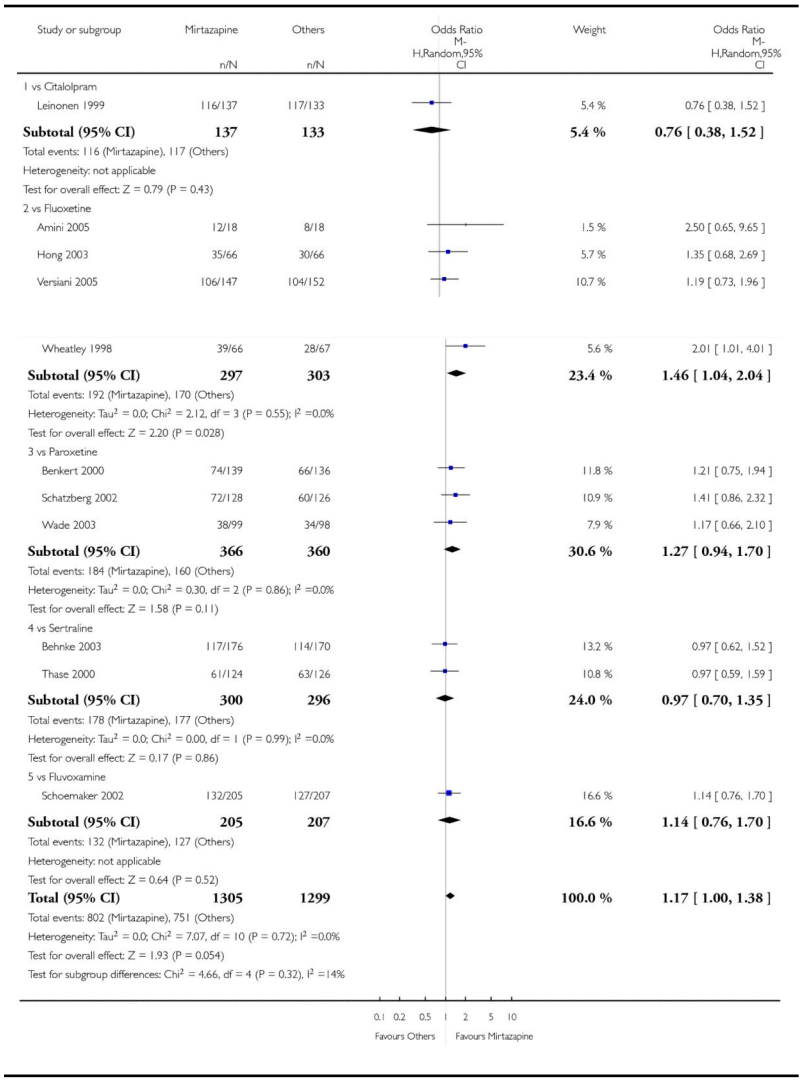
Analysis 2.30

Comparison 2 Mirtazapine versus SSRIs, Outcome 30 Sensitivity analysis: Response at end of the acute-phase treatment: Studies without imputation

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 2 Mirtazapine versus SSRIs

Outcome: 30 Sensitivity analysis: Response at end of the acute-phase treatment: Studies without imputation



Analysis 2.31

Comparison 2 Mirtazapine versus SSRIs, Outcome 31 Secondary outcome (SKEWED DATA: depression severity) at 2 weeks

Secondary outcome (SKEWED DATA: depression severity) at 2 weeks

Study	Comparator drug	Measurement	Mirtazapine: mean	SD	N	Comparator: mean	SD	N	note
Schoemaker 2002	Fluvoxamine	HAMD-17	−9.2	5.86	199	−7.3	6.11	203	
Winokur 2003	Fluoxetine	HAMD-21	16.1	5.7	8	18.0	9.6	11	

Analysis 2.32

Comparison 2 Mirtazapine versus SSRIs, Outcome 32 Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment

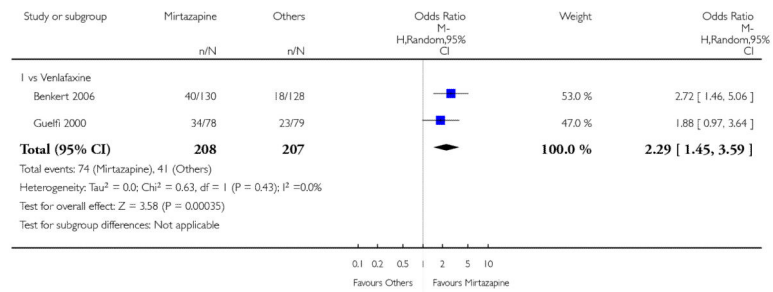
Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment

Study	Comparator drug	Measurement	Mirtazapine: mean	SD	N	Comparator: mean	SD	N	note
Schoemaker 2002	Fluvoxamine	HAMD-17	−14.3	7.33	199	−13.7	7.68	203	
Thase 2000	Sertraline	HAMD-17	8.7	7.6	119	10.5	7.2	124	
Winokur 2003	Fluoxetine	HAMD-21	7.1	3.7	8	12.2	9.2	11	

Analysis 3.1

Comparison 3 Mirtazapine versus SNRIs, Outcome 1 Primary outcome (response) at 2 weeks

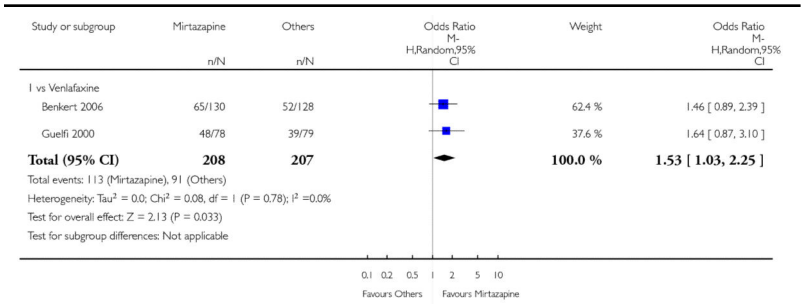
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 1 Primary outcome (response) at 2 weeks



Analysis 3.2

Comparison 3 Mirtazapine versus SNRIs, Outcome 2 Primary outcome (response) at end of the acute-phase treatment

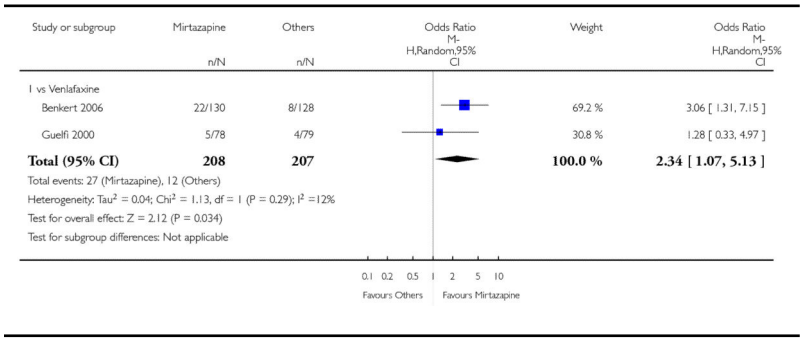
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 2 Primary outcome (response) at end of the acute-phase treatment



Analysis 3.3

Comparison 3 Mirtazapine versus SNRIs, Outcome 3 Secondary outcome (remission) at 2 weeks

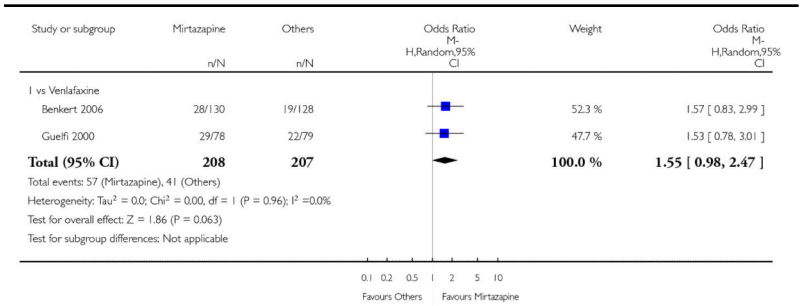
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 3 Secondary outcome (remission) at 2 weeks



Analysis 3.4

Comparison 3 Mirtazapine versus SNRIs, Outcome 4 Secondary outcome (remission) at end of the acute-phase treatment

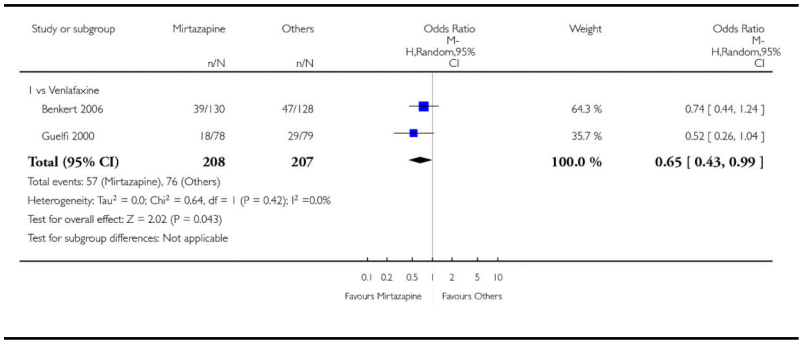
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 4 Secondary outcome (remission) at end of the acute-phase treatment



Analysis 3.5

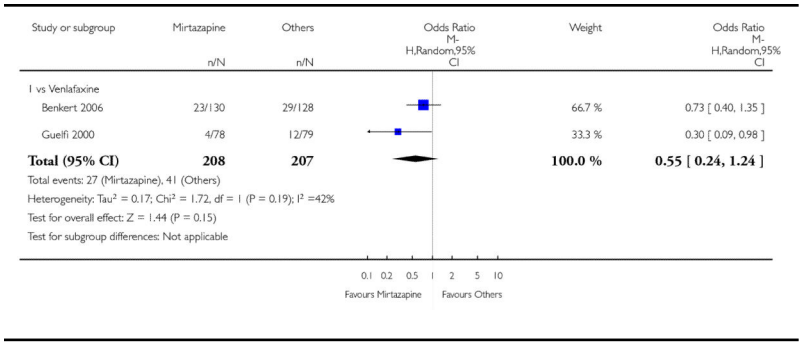
Comparison 3 Mirtazapine versus SNRIs, Outcome 5 Secondary outcome (withdrawal due to any reason)

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 5 Secondary outcome (withdrawal due to any reason)



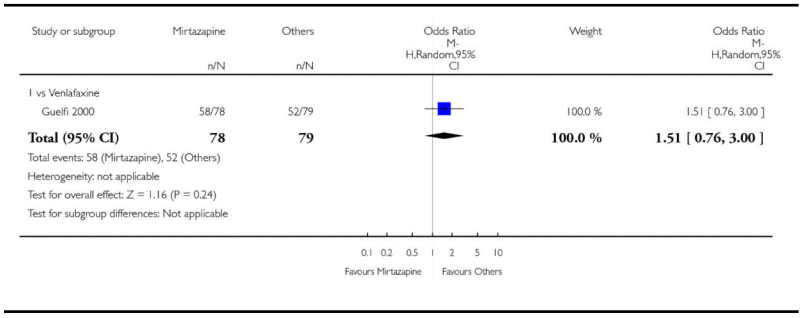
Analysis 3.6
Comparison 3 Mirtazapine versus SNRIs, Outcome 6
Secondary outcome (withdrawal due to adverse events)

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 6 Secondary outcome (withdrawal due to adverse events)



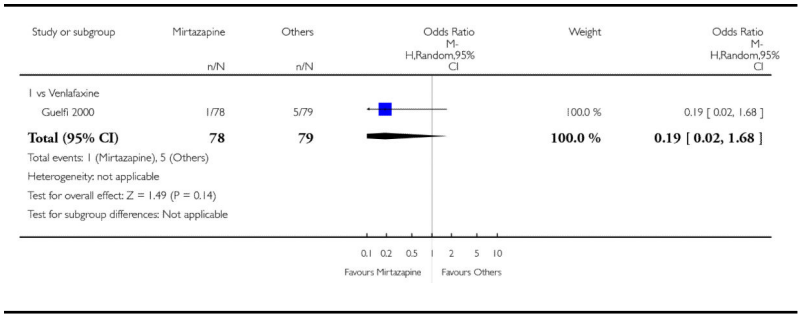
Analysis 3.7
Comparison 3 Mirtazapine versus SNRIs, Outcome 7
Secondary outcome (having some adverse events)

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 7 Secondary outcome (having some adverse events)



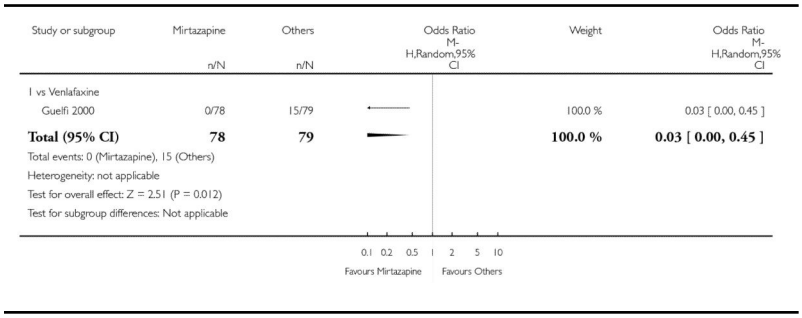
Analysis 3.8
Comparison 3 Mirtazapine versus SNRIs, Outcome 8 Hypotension/Bradycardia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 8 Hypotension/Bradycardia



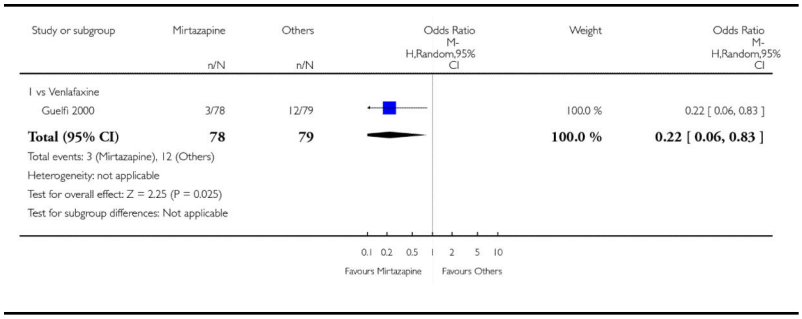
Analysis 3.9
Comparison 3 Mirtazapine versus SNRIs, Outcome 9 Sweating

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 9 Sweating



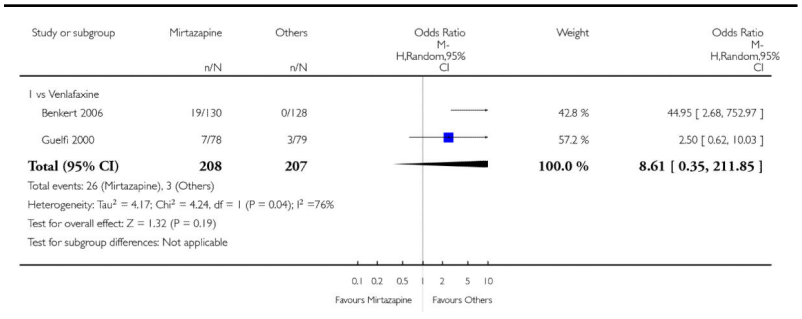
Analysis 3.10
Comparison 3 Mirtazapine versus SNRIs, Outcome 10 Constipation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 10 Constipation



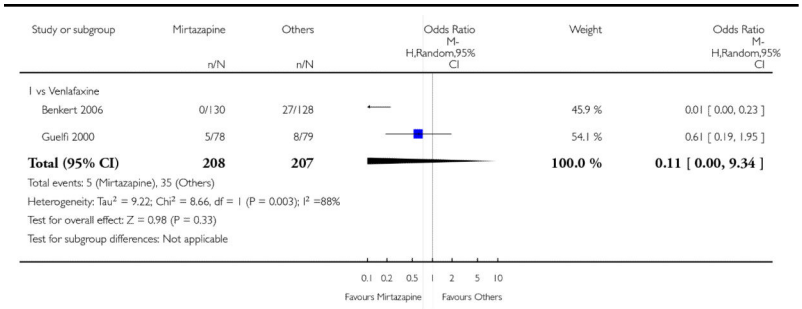
Analysis 3.11
Comparison 3 Mirtazapine versus SNRIs, Outcome 11 Dry mouth/Decreased salivation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 11 Dry mouth/Decreased salivation



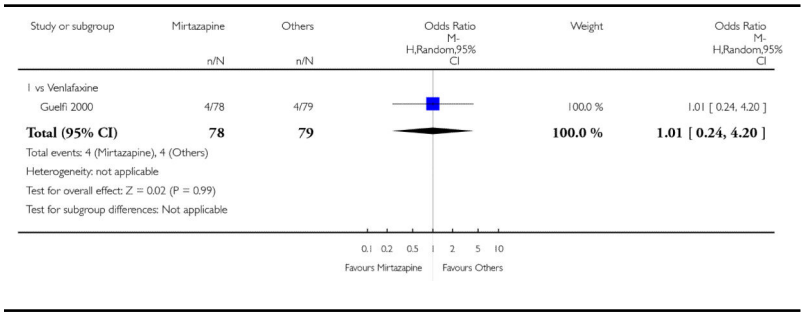
Analysis 3.12
Comparison 3 Mirtazapine versus SNRIs, Outcome 12 Nausea/Vomiting/Gastric distress

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 12 Nausea/Vomiting/Gastric distress



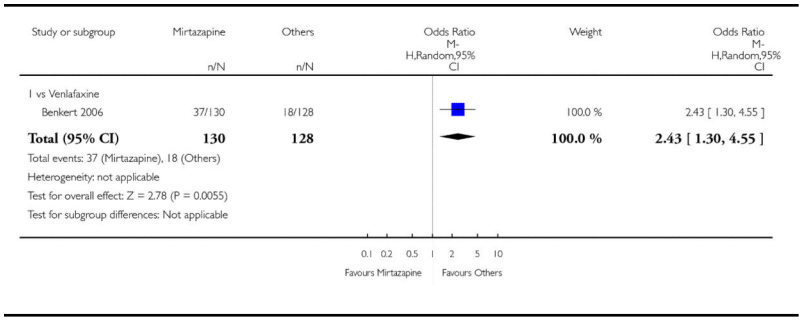
Analysis 3.13
Comparison 3 Mirtazapine versus SNRIs, Outcome 13 Anxiety/Agitation

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 13 Anxiety/Agitation



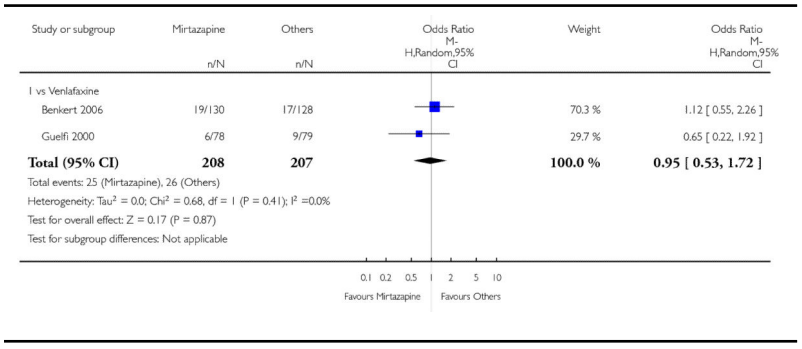
Analysis 3.14
Comparison 3 Mirtazapine versus SNRIs, Outcome 14 Fatigue/Tiredness/Asthenia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 14 Fatigue/Tiredness/Asthenia



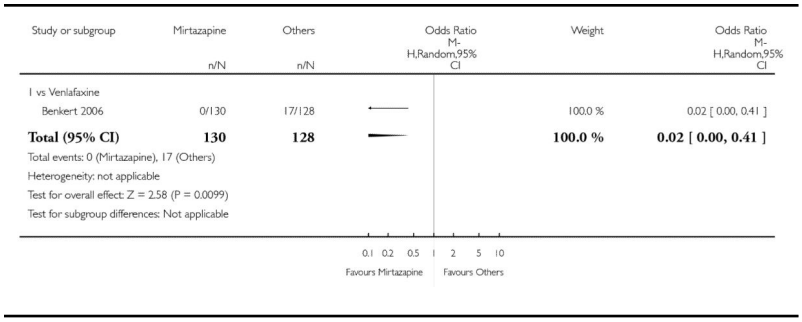
Analysis 3.15
Comparison 3 Mirtazapine versus SNRIs, Outcome 15 Headache

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 15 Headache



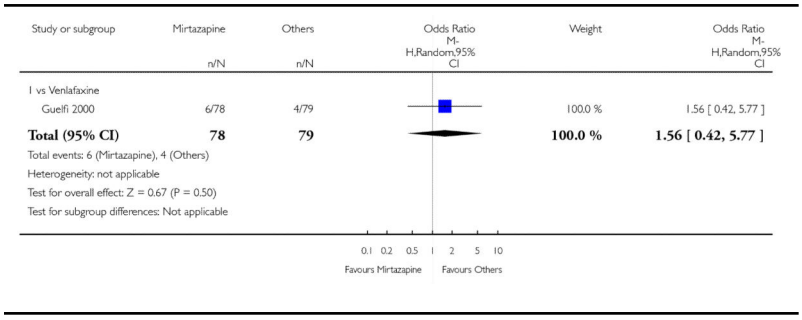
Analysis 3.16
Comparison 3 Mirtazapine versus SNRIs, Outcome 16 Sleep disturbance

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 16 Sleep disturbance



Analysis 3.17
Comparison 3 Mirtazapine versus SNRIs, Outcome 17 Sleepiness/Drowsiness/Somnolence

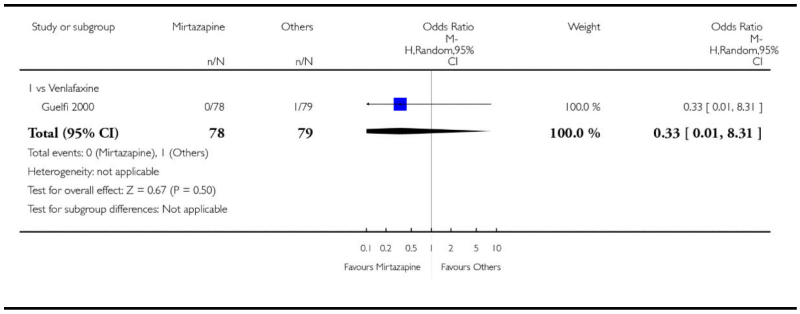
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 17 Sleepiness/Drowsiness/Somnolence



Analysis 3.18

Comparison 3 Mirtazapine versus SNRIs, Outcome 18 Completed suicide

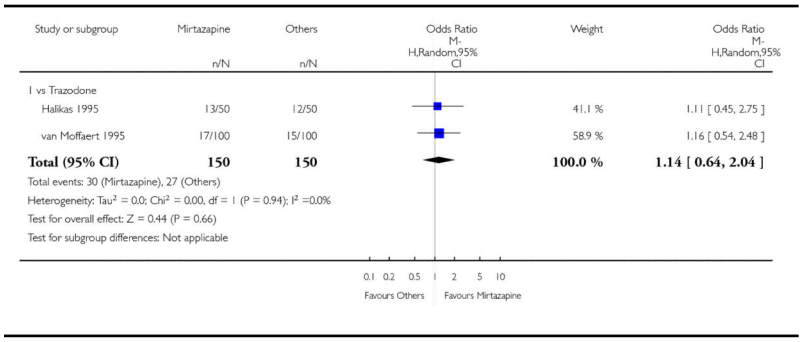
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 3 Mirtazapine versus SNRIs
Outcome: 18 Completed suicide



Analysis 4.1

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 1 Primary outcome (response) at 2 weeks

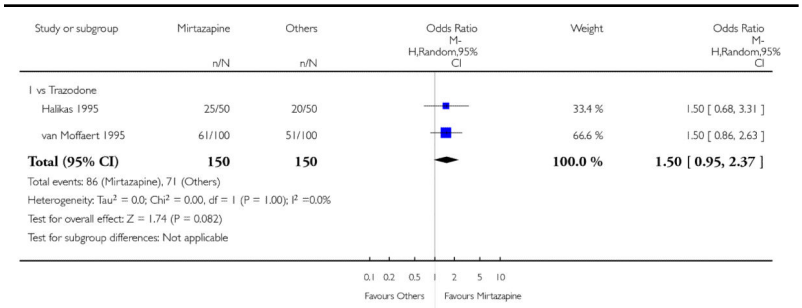
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 1 Primary outcome (response) at 2 weeks



Analysis 4.2

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 2 Primary outcome (response) at end of the acute-phase treatment

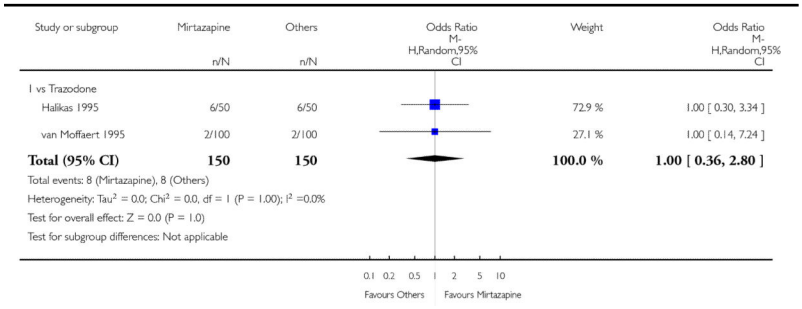
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 2 Primary outcome (response) at end of the acute-phase treatment



Analysis 4.3

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 3 Secondary outcome (remission) at 2 weeks

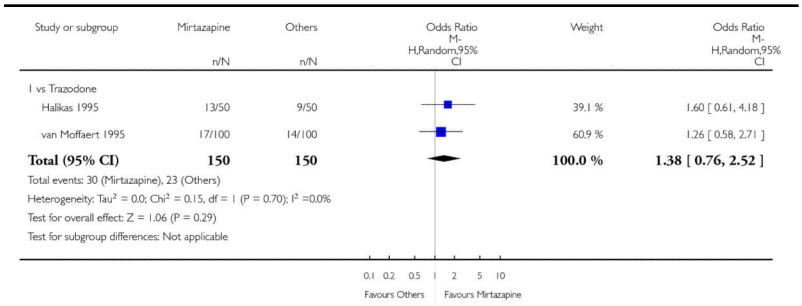
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 3 Secondary outcome (remission) at 2 weeks



Analysis 4.4

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 4 Secondary outcome (remission) at end of the acute-phase treatment

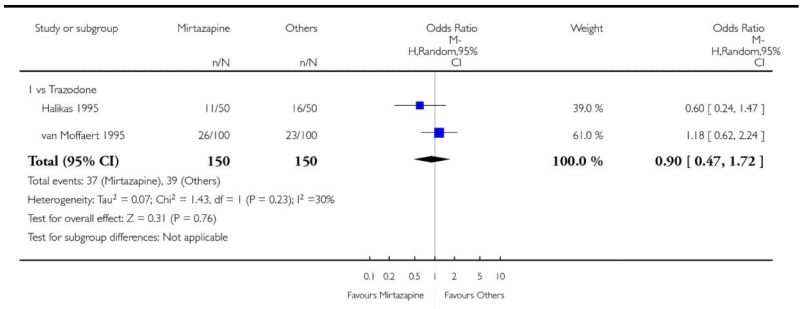
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 4 Secondary outcome (remission) at end of the acute-phase treatment



Analysis 4.5

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 5 Secondary outcome (withdrawal due to any reason)

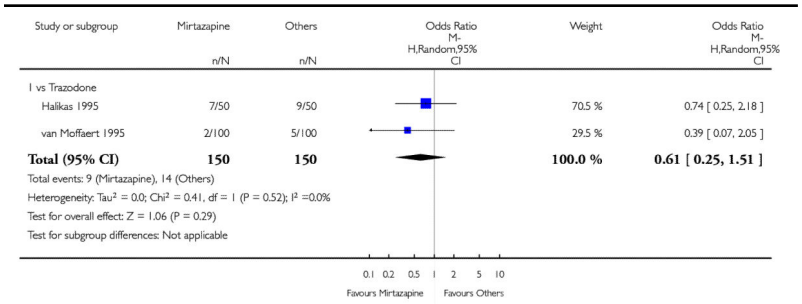
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 5 Secondary outcome (withdrawal due to any reason)



Analysis 4.6

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 6 Secondary outcome (withdrawal due to adverse events)

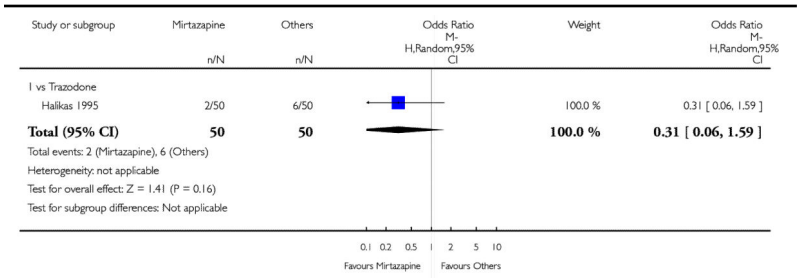
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 6 Secondary outcome (withdrawal due to adverse events)



Analysis 4.7

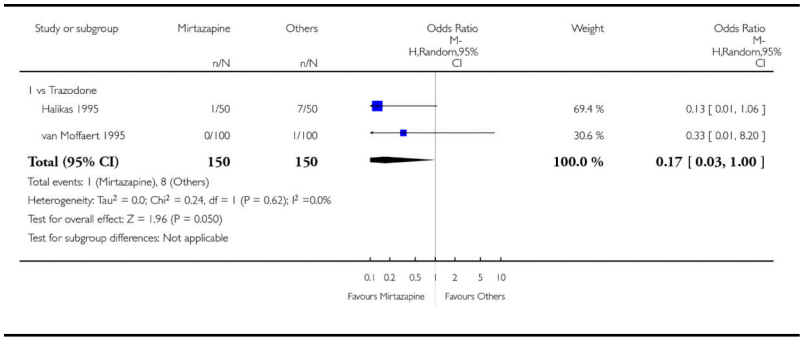
Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 7 Hypertension/Tachycardia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 7 Hypertension/Tachycardia



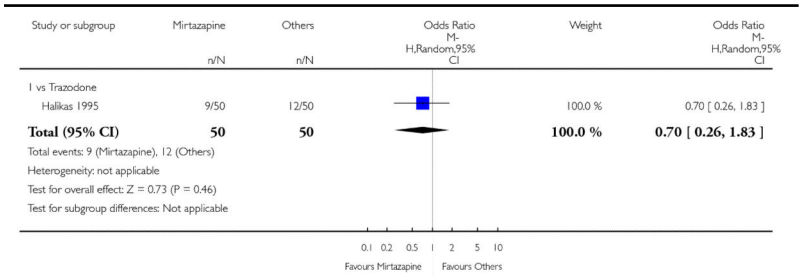
Analysis 4.8
Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 8 Hypotension/Bradycardia

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 8 Hypotension/Bradycardia



Analysis 4.9
Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 9 Constipation

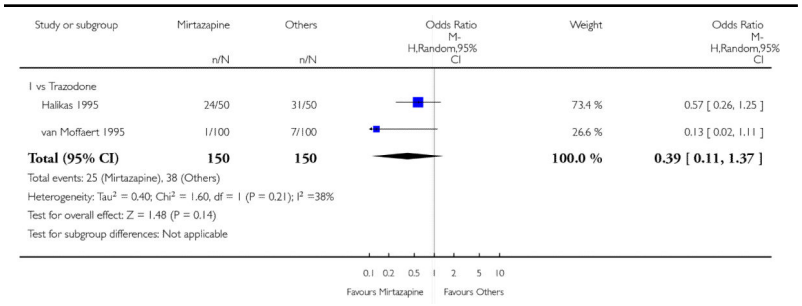
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 9 Constipation



Analysis 4.10

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 10 Dry mouth/Decreased salivation

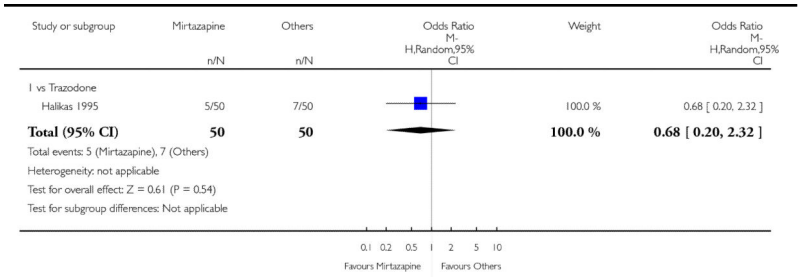
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 10 Dry mouth/Decreased salivation



Analysis 4.11

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 11 Nausea/Vomiting/Gastric distress

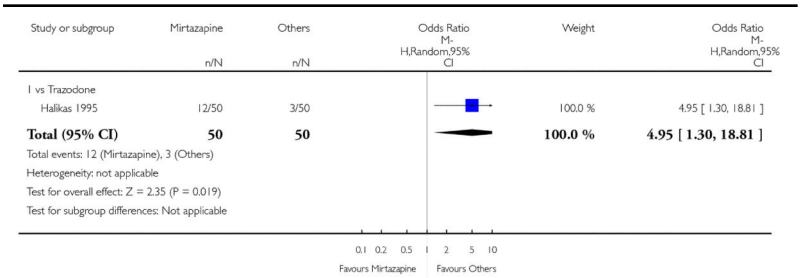
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 11 Nausea/Vomiting/Gastric distress



Analysis 4.12

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 12Weight gain/Increased appetite

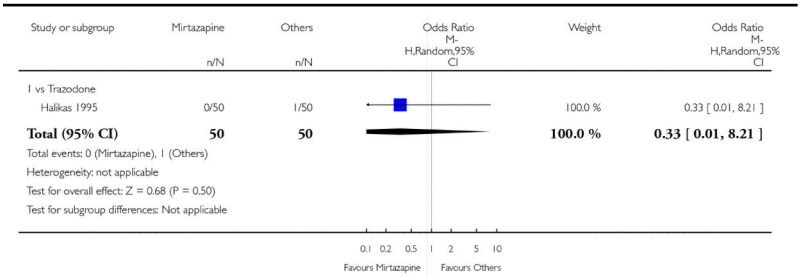
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 12 Weight gain/Increased appetite



Analysis 4.13

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 13Weight loss/Anorexia

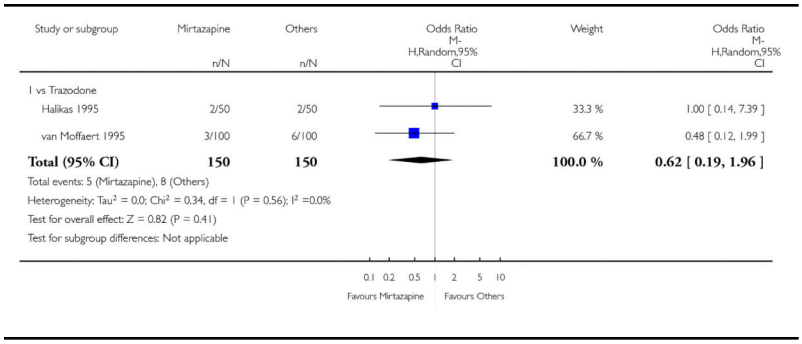
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 13 Weight loss/Anorexia



Analysis 4.14

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 14 Anxiety/Agitation

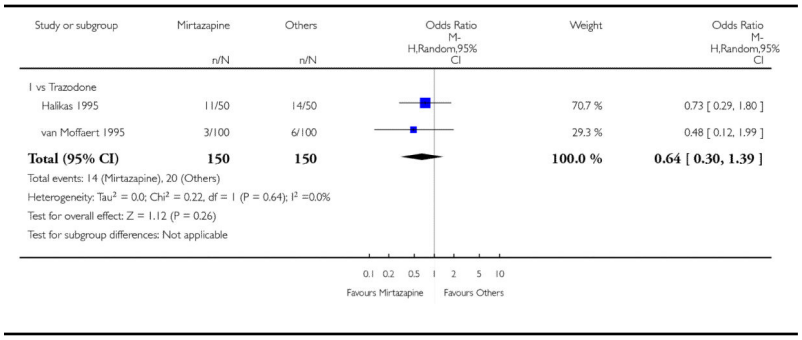
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 14 Anxiety/Agitation



Analysis 4.15

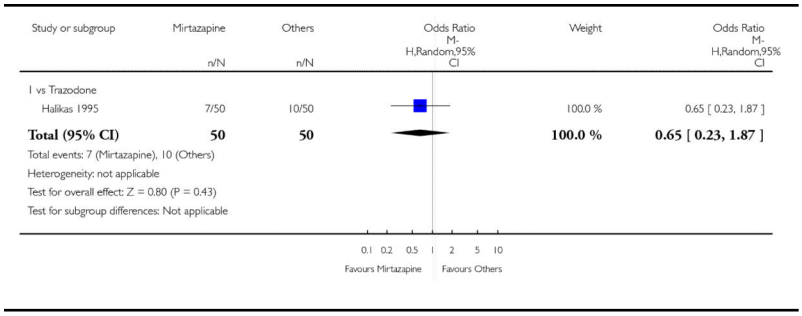
Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 15 Dizziness/Vertigo/ Faintness

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 15 Dizziness/Vertigo/Faintness



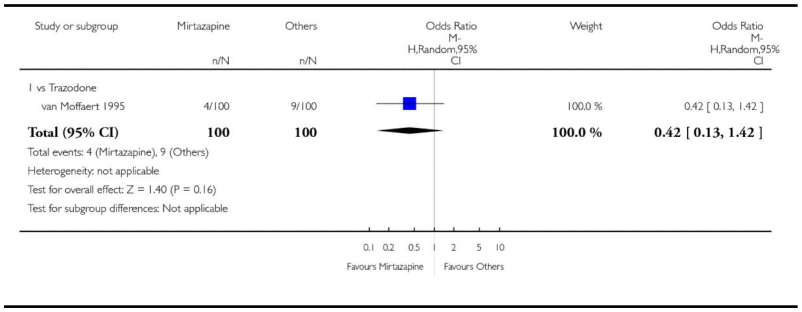
Analysis 4.16
Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 16 Headache

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 16 Headache



Analysis 4.17
Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 17 Sleep disturbance

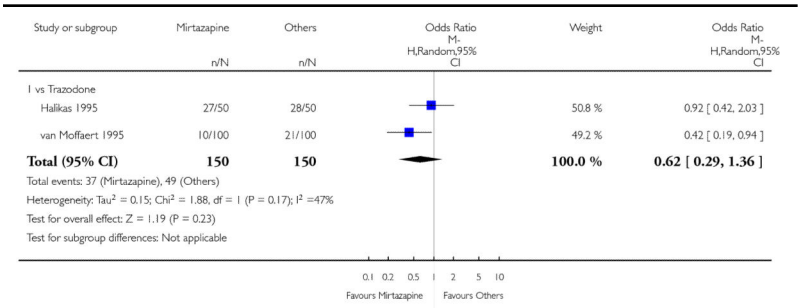
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 17 Sleep disturbance



Analysis 4.18

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 18 Sleepiness/Drowsiness/ Somnolence

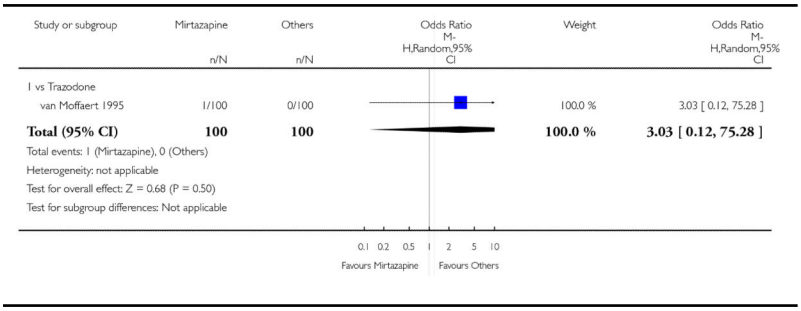
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 18 Sleepiness/Drowsiness/Somnolence



Analysis 4.19

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 19 Completed suicide

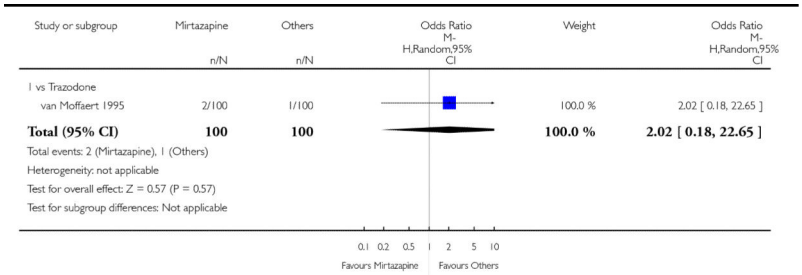
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 19 Completed suicide



Analysis 4.20

Comparison 4 Mirtazapine versus heterocyclic antidepressants, Outcome 20 Suicide attempt

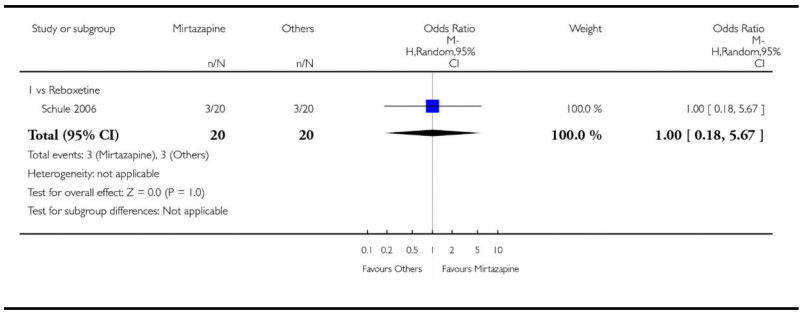
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 4 Mirtazapine versus heterocyclic antidepressants
Outcome: 20 Suicide attempt



Analysis 5.1

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 1 Primary outcome (response) at 2 weeks

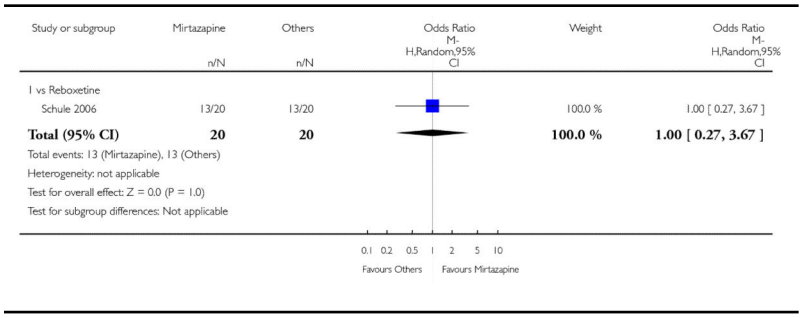
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 1 Primary outcome (response) at 2 weeks



Analysis 5.2

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 2 Primary outcome (response) at end of the acute-phase treatment

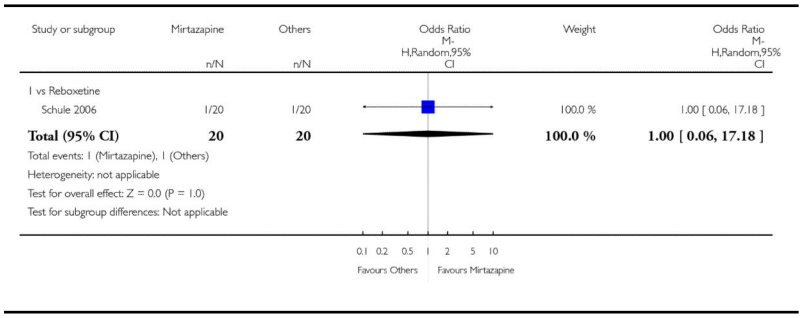
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 2 Primary outcome (response) at end of the acute-phase treatment



Analysis 5.3

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 3 Secondary outcome (remission) at 2 weeks

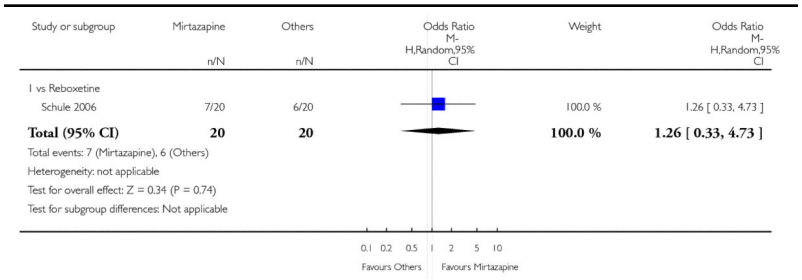
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 3 Secondary outcome (remission) at 2 weeks



Analysis 5.4

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 4 Secondary outcome (remission) at end of the acute-phase treatment

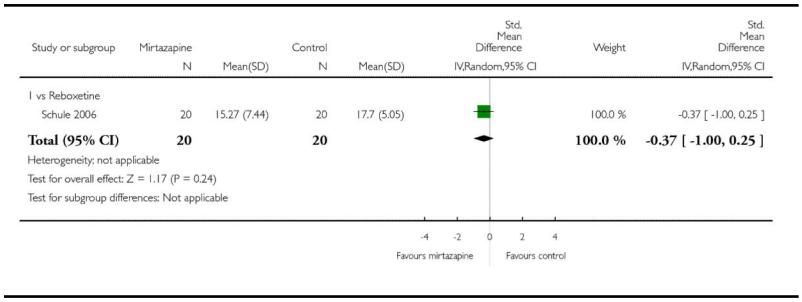
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 4 Secondary outcome (remission) at end of the acute-phase treatment



Analysis 5.5

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 5 Secondary outcome (depression severity) at 2 weeks

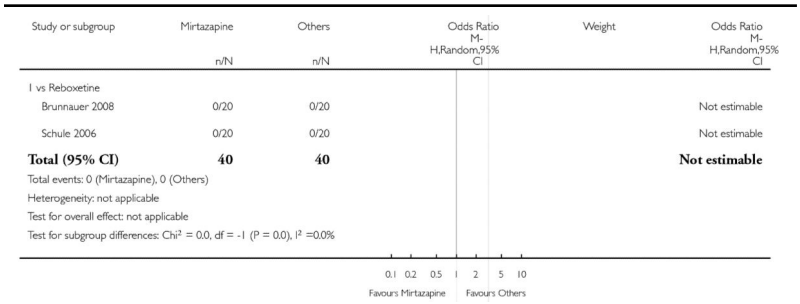
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 5 Secondary outcome (depression severity) at 2 weeks



Analysis 5.6

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 6 Secondary outcome (withdrawal due to any reason)

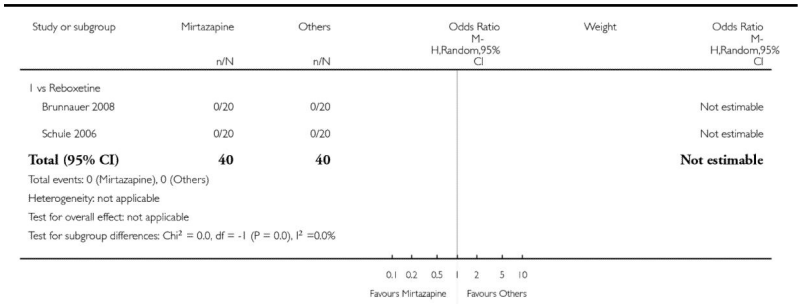
Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 6 Secondary outcome (withdrawal due to any reason)



Analysis 5.7

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 7 Secondary outcome (withdrawal due to adverse events)

Review: Mirtazapine versus other antidepressive agents for depression
Comparison: 5 Mirtazapine versus newer antidepressants
Outcome: 7 Secondary outcome (withdrawal due to adverse events)



Analysis 5.8

Comparison 5 Mirtazapine versus newer antidepressants, Outcome 8 Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment

Secondary outcome (SKEWED DATA: depression severity) at end of the acute-phase treatment

Study	Comparator drug	Measurement	Mirtazapine: mean	SD	N	Comparator: mean	SD	N	note
Schule 2006	Reboxetine	21-item HAM-D	10.87	6.91	20	11.17	6.17	20	

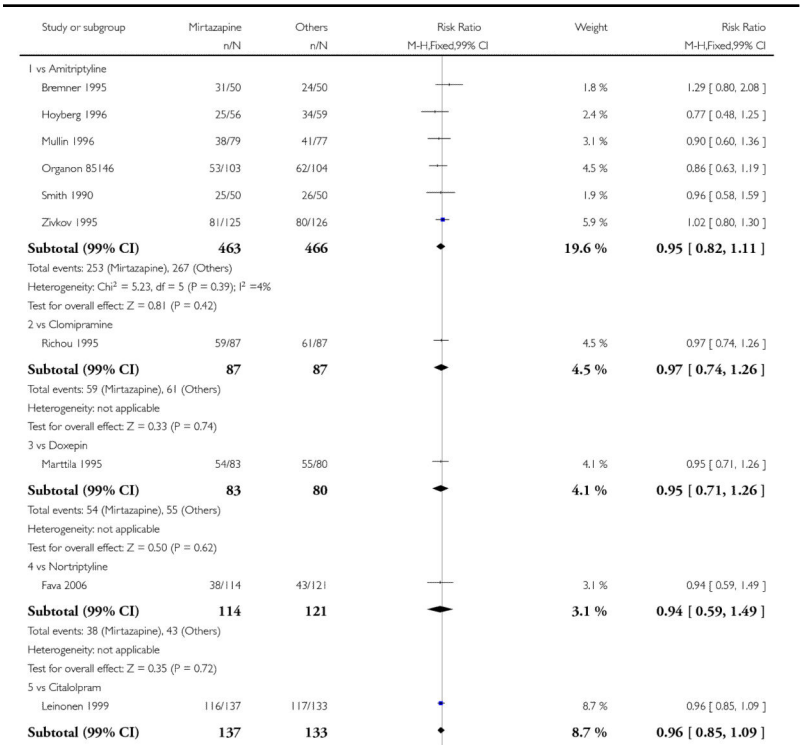
Analysis 6.1

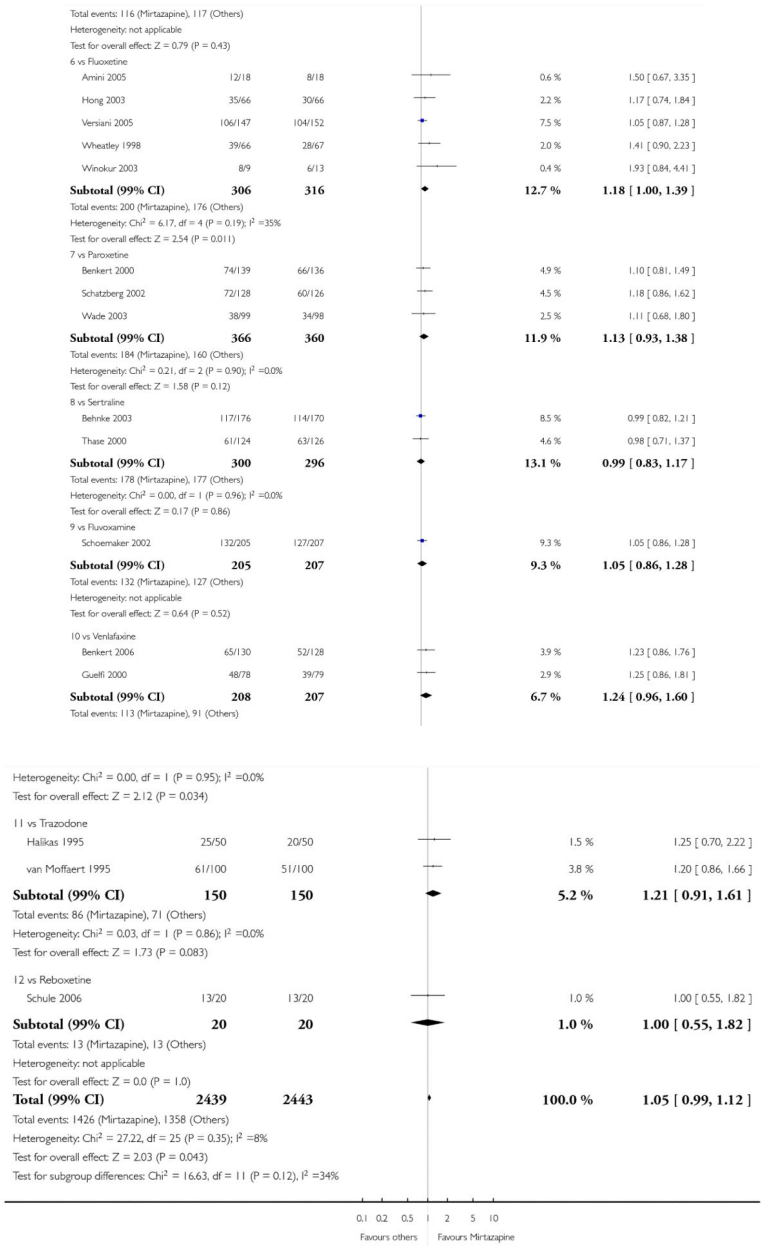
Comparison 6 Funnel plot analysis: primary outcome (response) at end of the acute-phase treatment, Outcome 1 vs all compounds

Review: Mirtazapine versus other antidepressive agents for depression

Comparison: 6 Funnel plot analysis: primary outcome (response) at end of the acute-phase treatment

Outcome: 1 vs all compounds





HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 12, 2011

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The definition of the early response rates has been amended from that in the published protocol ("Early response rates: between 1 and 4 weeks, the time point closest to 2 weeks will be given preference"), because, after starting the review process, we recognised that all trials reported outcomes at 2 weeks when trials gave information about early response rate.

The subgroup analyses have been amended from the published protocol in which there are five subgroup analyses (mirtazapine dosing, comparator dosing, depression severity, treatment settings, elderly participants). The sensitivity analyses have been amended from the published protocol in which there are six sensitivity analyses (excluding trials with unclear concealment of random allocation or unclear double blinding, excluding trials whose dropout rate is greater than 20%, performing the worst case and best case scenario ITT, excluding trials for which the response rates had to be calculated based on the imputation method or borrowed from other trials, examination of 'wish bias' by comparing mirtazapine as investigational drug versus mirtazapine as comparator, excluding studies funded by the pharmaceutical company marketing mirtazapine).

These planned but not conducted analyses will be done in future updates of the review if adequate numbers of studies are available for the analyses.

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

Mirtazapine versus other antidepressive agents for depression

Major depression is characterised by a persistent low mood and loss of interest and pleasure. These symptoms are often accompanied by loss of appetite, insomnia, fatigue, poor concentration, inappropriate guilty feelings and even suicide. Depression was the third leading cause of disease burden among all diseases experienced by humankind in 2002. Antidepressants are used in treatment for major depression. They are the mainstay of treatment. Among them, mirtazapine is known to have a unique pharmacological profile and thus is supposed to differ in its efficacy and adverse effects profile in comparison with other antidepressants.

The evidence from this review, which included findings from 29 randomised controlled trials (4974 participants in total), suggests that mirtazapine is likely to have a faster onset of action than the most frequently used type of antidepressants, which are the selective serotonin reuptake inhibitors (SSRIs). It would appear that mirtazapine is superior to SSRIs at the end of treatment over 6 to 12 weeks. Mirtazapine causes adverse events that lead to a similar frequency of dropouts as SSRIs and tricyclic antidepressants, although adverse event profile of mirtazapine is unique. Mirtazapine is likely to cause weight gain or increased appetite and somnolence but is less likely to cause nausea or vomiting and sexual dysfunction than SSRIs.

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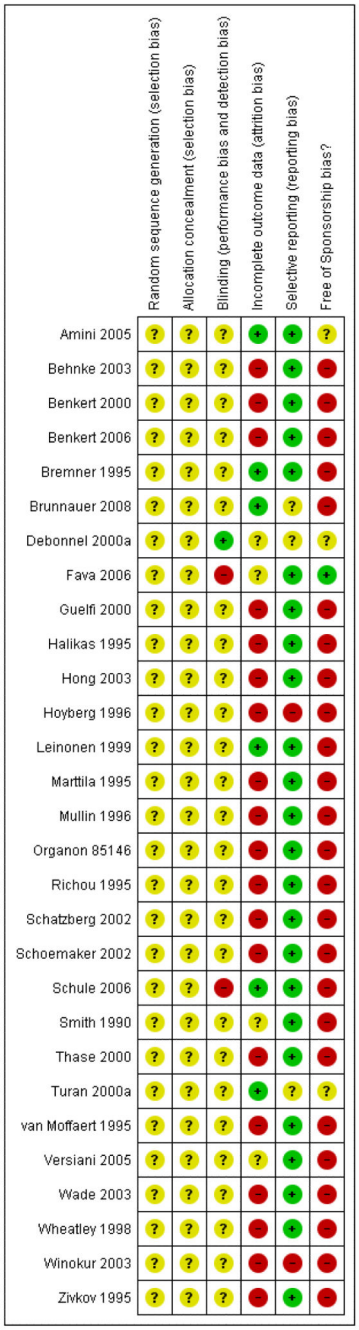

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

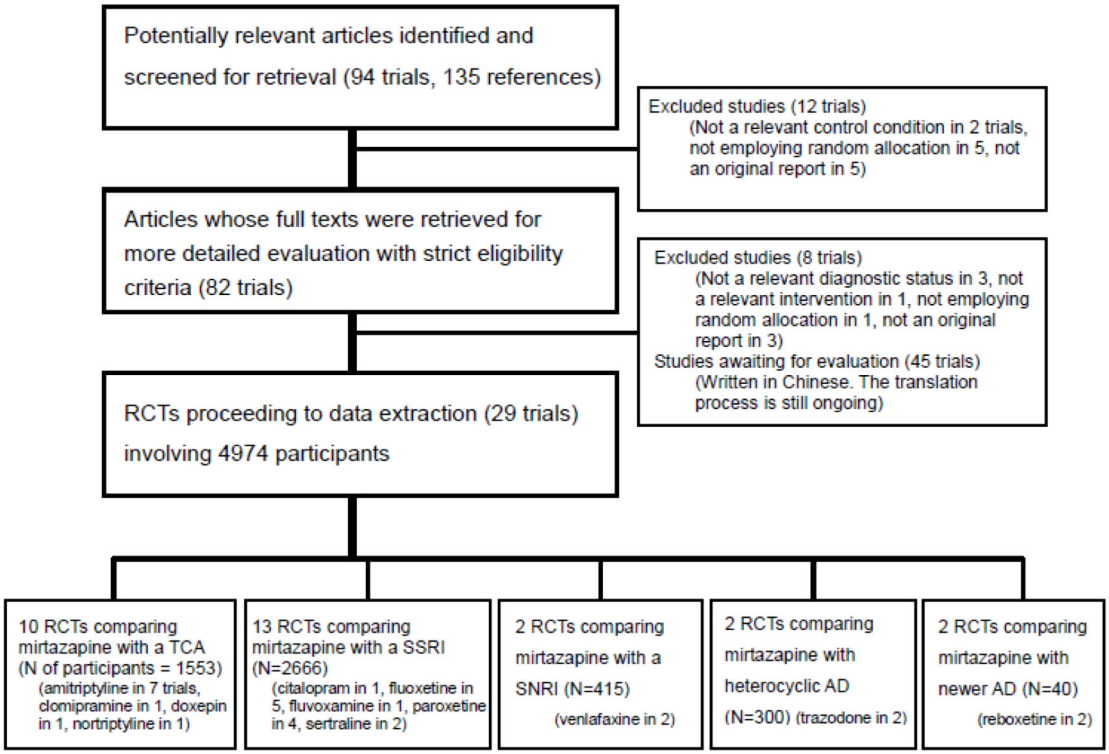

Figure 2.

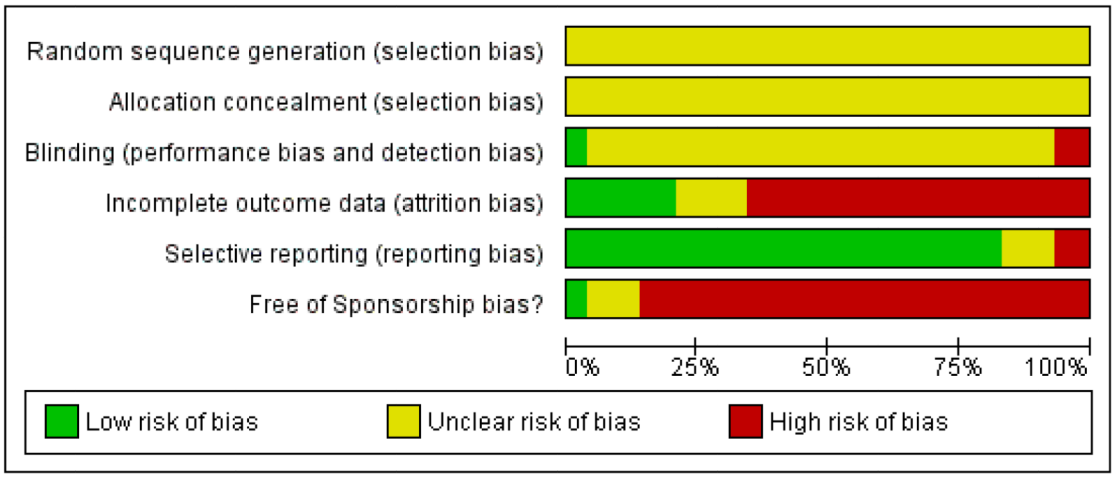

Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

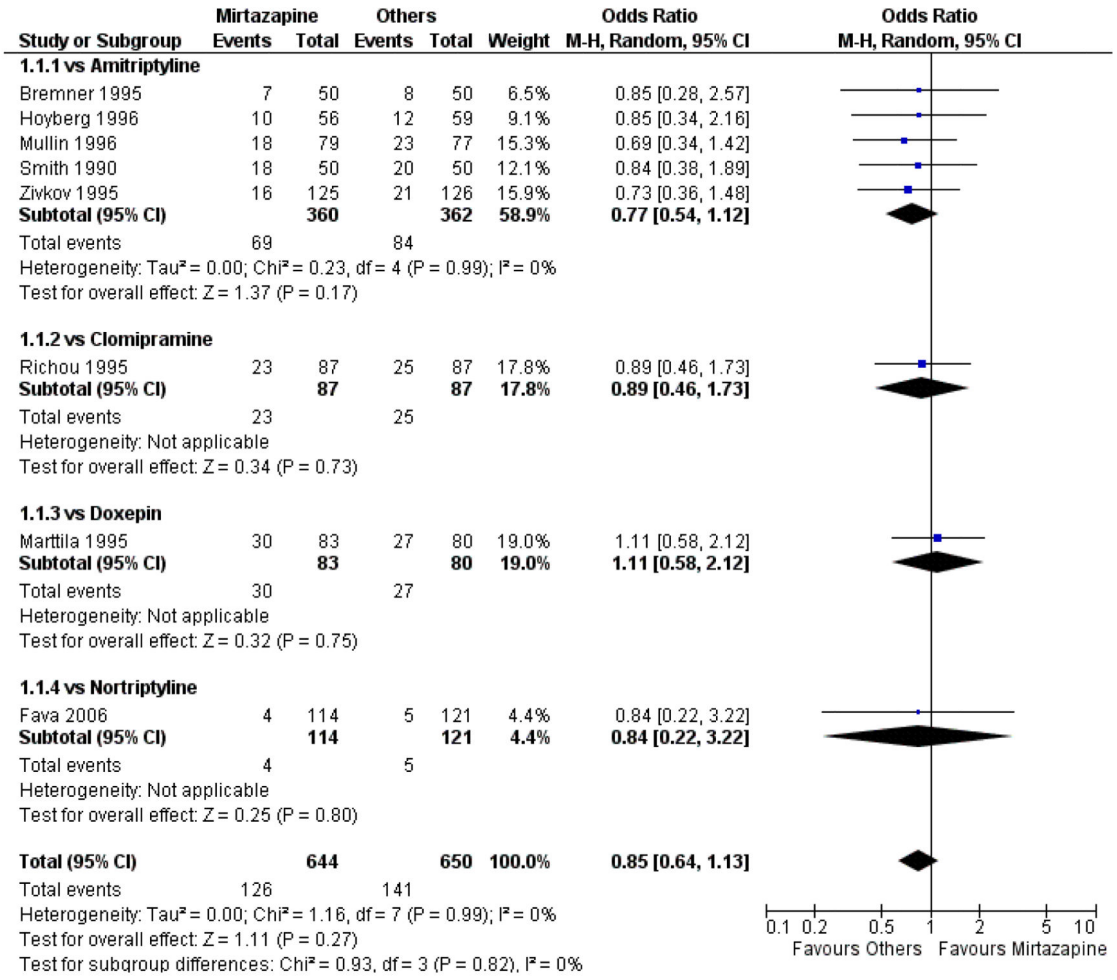

Figure 4. Forest plot of comparison: 1 MIRTAZAPINE vs TCAs, outcome: 1.1 Primary outcome (response) at 2 weeks

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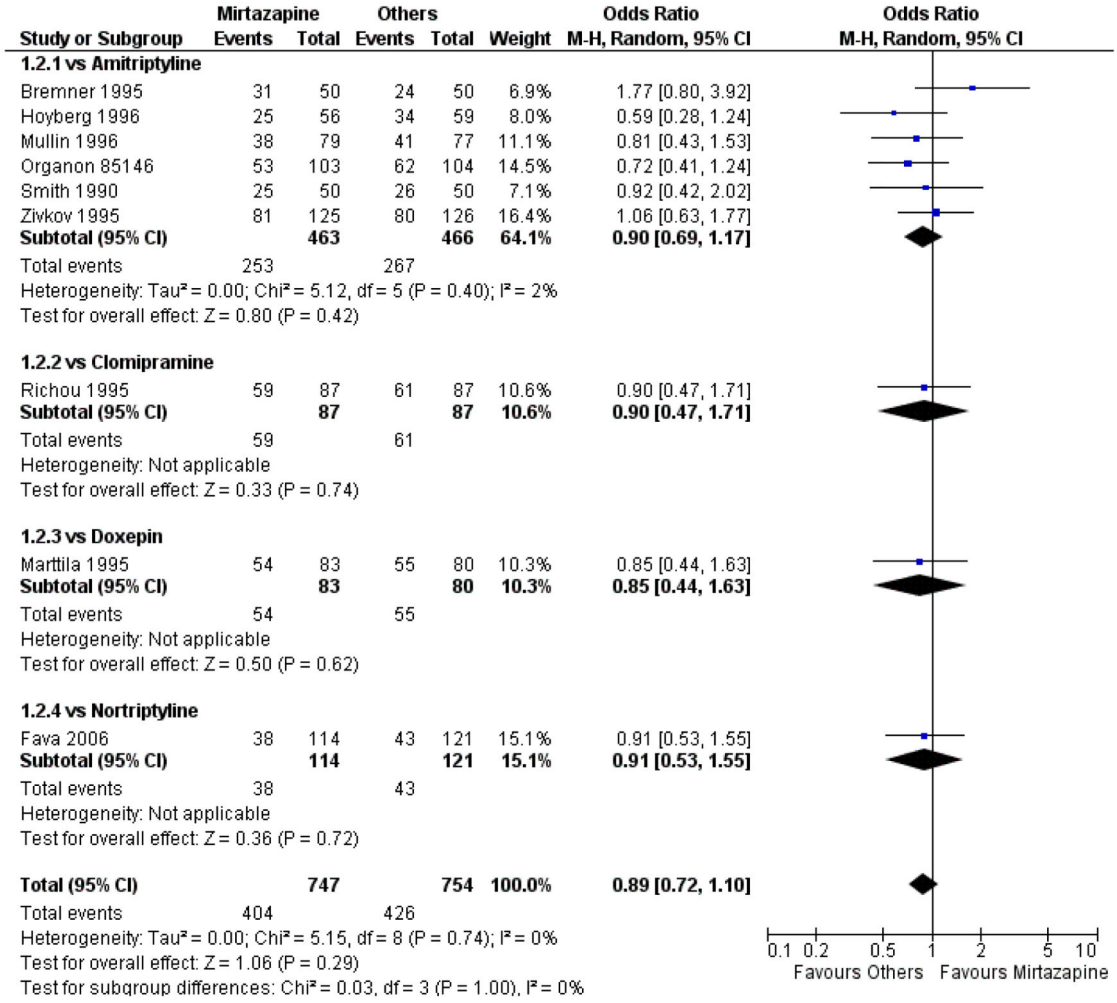

Figure 5. Forest plot of comparison: 1 MIRTAZAPINE vs TCAs, outcome: 1.2 Primary outcome (response) at end of the acute-phase treatment

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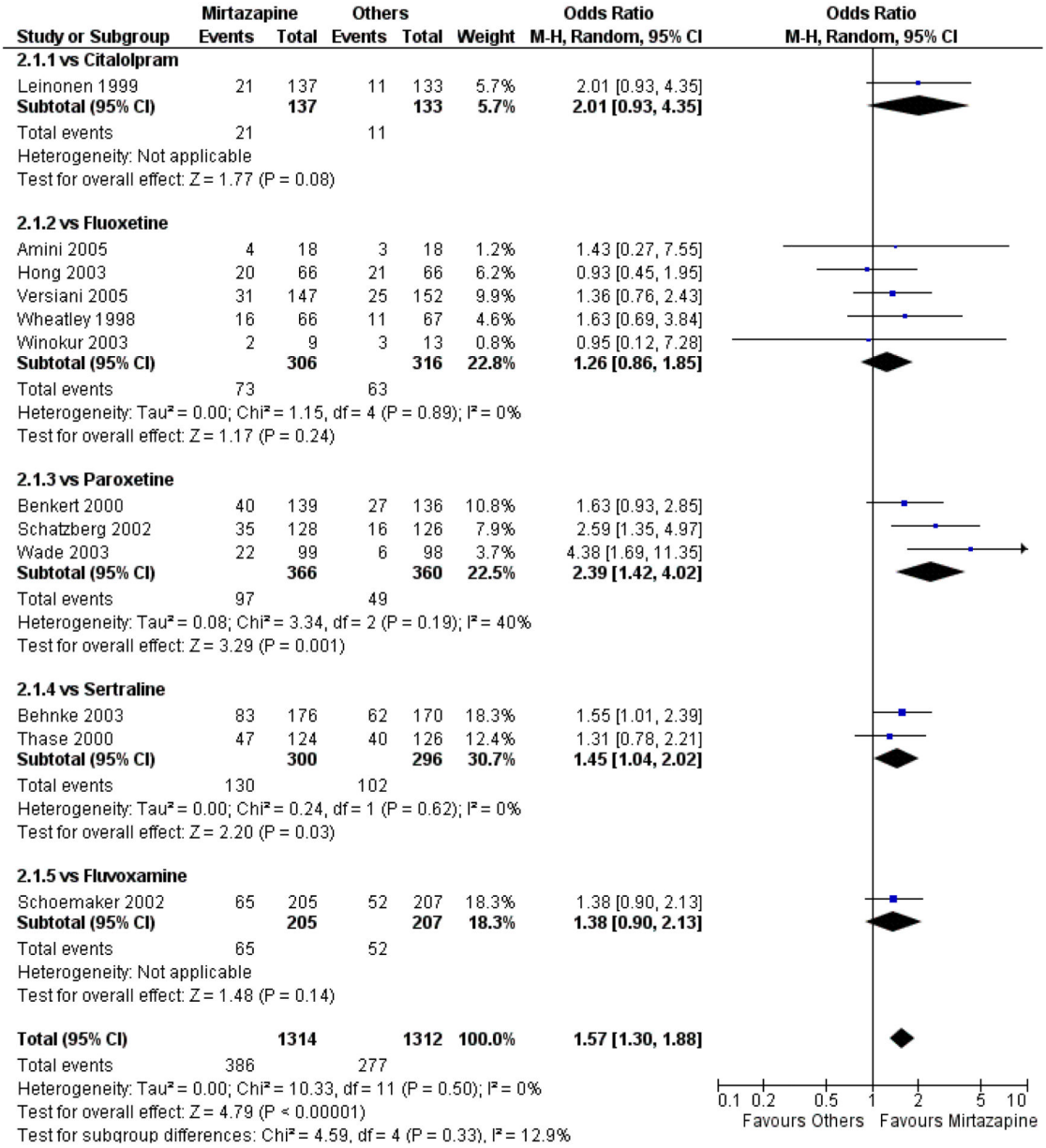

Figure 6. Forest plot of comparison: 2 MIRTAZAPINE vs SSRIs, outcome: 2.1 Primary outcome (response) at 2 weeks

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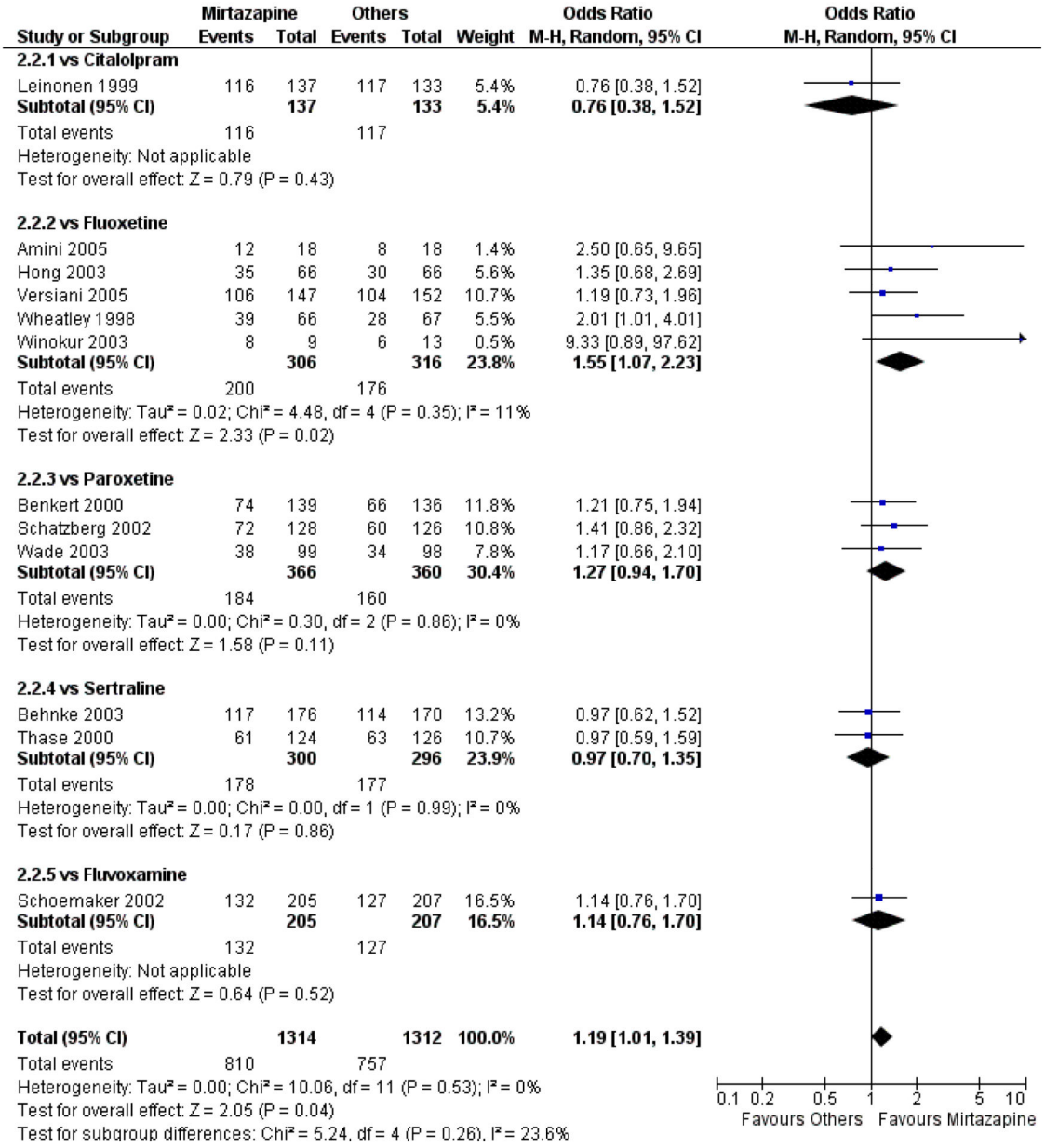

Figure 7. Forest plot of comparison: 2 MIRTAZAPINE vs SSRIs, outcome: 2.2 Primary outcome (response) at end of the acute-phase treatment

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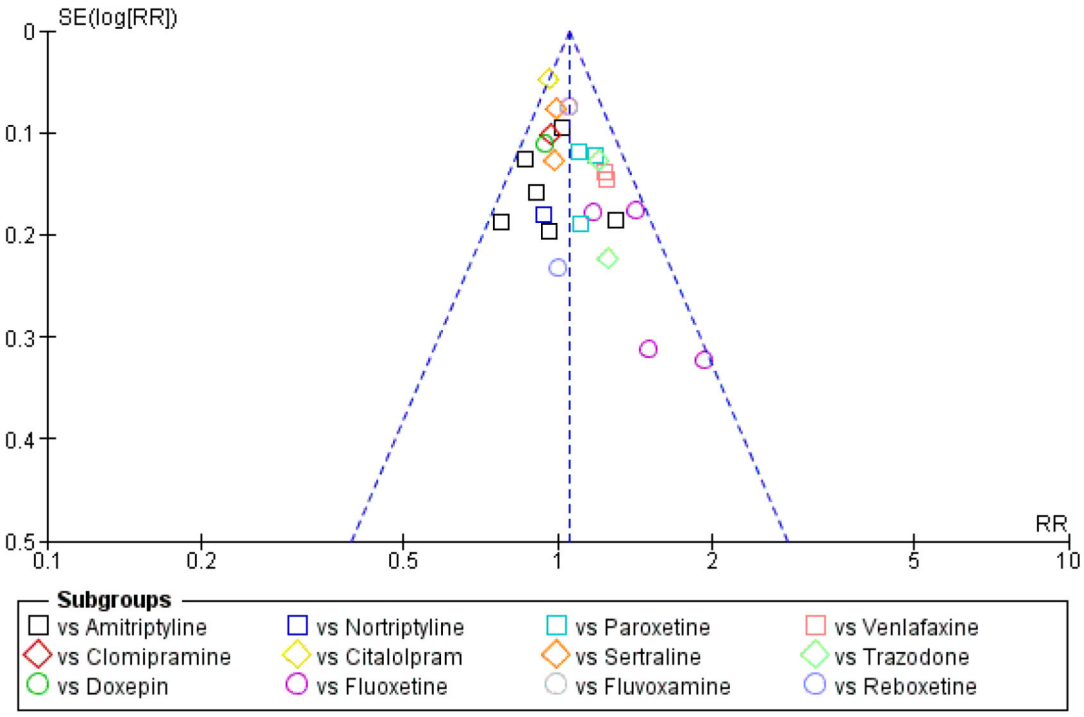

Figure 8. Funnel plot of comparison: 6 Funnel plot analysis: Primary outcome (response) at end of the acute-phase treatment, outcome: 6.1 vs all compounds

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